Cosmetic Dermatology

Products and Procedures

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Third Edition

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WILEY Blackwell

This edition first published 2022

Edition History
John Wiley & Sons, Ltd (2e, 2016); Blackwell Publishing, Ltd (1e, 2010)

Registered Offices
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data

Names: Draelos, Zoe Diana, editor.
Title: Cosmetic dermatology : products and procedures / Zoe Diana Draelos,
MD, Consulting Professor Department of Dermatology Duke University
School of Medicine Durham, NC, USA.
Description: Third edition. | Hoboken : Wiley, 2022. | Includes index.
Identifiers: LCCN 2021027308 (print) | LCCN 2021027309 (ebook) | ISBN 9781119676836 (hardback) |
ISBN 9781119676768 (adobe pdf) | ISBN 9781119676867 (epub)
Subjects: LCSH: Skin–Care and hygiene. | Cosmetics. | Dermatology.
Classification: LCC RL87 .C68 2021 (print) | LCC RL87 (ebook) | DDC 646.7/2–dc23
LC record available at https://lccn.loc.gov/2021027308
LC ebook record available at https://lccn.loc.gov/2021027309

Cover Design: Wiley
Cover Images: © Micro Discovery/Getty Images, Hillary Kladke/Getty Images, SCIENCE PHOTO LIBRARY/Getty Images, LaylaBird/E+/Getty Images

Set in 9.5/12pt Minion by Straive, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

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Foreword

Advances in the field of cosmeceuticals over the past 20 years have been quite staggering. Since Zoe Draelos published her first Cosmetic Dermatology: Products and Procedures in 2009 there has been exponential understanding of the field and explosion of products. And not surprisingly, Dr. Draelos has been at the forefront pioneering research in this burgeoning field.

To be fair, the areas of cosmetic procedures and cosmeceuticals were more of an art form than a science when Dr. Draelos and I started our careers in dermatology. She, along with her colleagues around the world, has been instrumental in helping our understanding of the many benefits of cosmeceuticals.

There is no better way to truly learn of the many products and procedures in cosmetic dermatology than using Dr. Draelos's textbook as a guide. Enjoy it in a piecemeal fashion or read it cover to cover. You don't want to be without it if you are practicing dermatology in the 2020s. I know I sure don't!

Jeffrey S. Dover
Boston, MA, USA

Preface

This text is intended to function as a compendium on the field of cosmetic dermatology. Cosmetic dermatology knowledge draws on the insights of the bench researcher, the innovation of the manufacturer, the formulation expertise of the cosmetic chemist, the art of the dermatologic surgeon, and the experience of the clinical dermatologist. These knowledge bases heretofore have been presented in separate textbooks written for specific audiences. This silo organization of knowledge does not provide for the information synthesis required to advance the science of cosmetic dermatology. Only by combining these databases can new innovation occur.

The book begins with a discussion of basic concepts relating to skin physiology. The areas of skin physiology those are relevant to cosmetic dermatology including skin barrier, photoaging, sensitive skin, pigmentation issues, and sensory perceptions. All cosmetic products impact the skin barrier with the intention of improving skin health. Failure of the skin to function optimally results in photoaging, sensitive skin, dyspigmentation, and allergic/irritant contact dermatitis. While the dermatologist can assess skin health visually, noninvasive methods are valuable to confirm observations or to detect slight changes in skin health that are imperceptible to the human eye.

An important part of cosmetic dermatology products is the manner in which they are presented to the skin surface. Delivery systems are key to product efficacy and include creams, ointments, aerosols, powders, and nanoparticles. Once delivered to the skin surface, those substances designed to modify the skin must penetrate with aid of penetration enhancers to ensure percutaneous delivery.

The most useful manner to evaluate products used in cosmetic dermatology is categorization. The book is organized by product, based on the order in which they are used as part of a daily routine. The first daily activity is cleansing to ensure proper hygiene. A variety of cleansers are available to maintain the biofilm and microbiome to include bars, body washes, facial cleansers, hands cleansers, and shampoos.

Following cleansing, the next step is typically moisturization. There are unique moisturizers for the face, hands, and feet. Extensions of moisturizers that contain other active ingredients include sunscreens. Other products with a unique hygiene purpose include antiperspirants and shaving products.

The book then turns to colored products for adorning the body. These include colored facial cosmetics, namely facial foundations, lipsticks, and eye cosmetics. It is the artistic use of these cosmetics that can provide camouflaging for skin abnormalities of contour and color. Adornment can also be applied to the nails, in the forms of nail cosmetics and prostheses, and to the hair, in the form of hair dyes, permanent waves, and hair straightening.

From adornment, the book addresses the burgeoning category of cosmeceuticals. Cosmeceuticals can be divided into the broad categories of botanicals, antioxidants, peptides, growth factors, retinoids, exfoliants, and topical vitamins. Oral vitamins are also important in appearance. These topical and oral agents aim to improve the aging skin appearance, however injectable products for rejuvenation, to include neurotoxins and fillers, are dominant forces in antiaging medicine.

The surgical aspects of cosmetic dermatology are addressed in terms of resurfacing and skin modulation techniques. Resurfacing can be accomplished chemically with superficial and medium depth chemical peels or physically with dermabrasion, ablative lasers, and nonablative lasers. Collagen regeneration can be achieved thermally with radiofrequency or through growth factors concentrated in platelet rich plasma.

Finally, the book closes with a discussion of how cosmetic dermatology can be implemented as part of a treatment regimen for aging skin, acne, rosacea, psoriasis, and eczema.

In order to allow effective synthesis of the wide range of information included in this text, each chapter has been organized with a template to create a standardized presentation. It is my hope this work will provide a standard textbook for the broad field of cosmetic dermatology inspiring thought, discussion, innovation, and joy!

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PART I

Basic Concepts

SECTION 1

Skin Physiology Pertinent to Cosmetic Dermatology

CHAPTER 1

Epidermal Barrier

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BASIC CONCEPTS

- The outermost structure of the epidermis is the stratum corneum (SC), and it forms the epidermal permeability barrier which prevents the loss of water and electrolytes.
- Understanding the structure and function of the stratum corneum and the epidermal barrier is vital because it is the key to healthy skin.
- Novel delivery systems play an increasingly important role in the development of effective skin care products. Delivery technologies such as lipid systems, nanoparticles, microcapsules, polymers, and films are being pursued.
- Cosmetic companies will exploit this new knowledge in developing more efficacious products for strengthening the epidermal barrier and to enhance the functional and aesthetic properties of the skin.

Introduction

Skin is the interface between the body and the environment. There are three major compartments of the skin, the epidermis, dermis, and the hypodermis. Epidermis is the outermost structure and it is a multilayered epithelial tissue divided into several layers. The outermost structure of the epidermis is the stratum corneum (SC), and it forms the epidermal permeability barrier which prevents the loss of water and electrolytes. Other protective/barrier roles for the epidermis include immune defense, UV protection, and protection from oxidative damage. Changes in the epidermal barrier caused by environmental factors, age, or other conditions can alter the appearance as well as the functions of the skin. Understanding the structure and function of the SC and the epidermal barrier is vital because it is the key to healthy skin and its associated social ramifications.

Structural components of the epidermal barrier

The outer surface of the skin, the epidermis, mostly consists of epidermal cells, known as keratinocytes, that are arranged in several *stratified* layers – the basal cell layer, the spinous cell layer, *and* the granular cell layer whose differentiation eventually produces the SC. Unlike other layers, SC is made of anucleated cells called corneocytes that are derived from keratinocytes. SC forms the major protective barrier of the skin, the epidermal permeability barrier. Figure 1.1 shows the different layers of the epidermis and the components that form the epidermal barrier. SC is a structurally heterogeneous tissue composed of nonnucleated, flat, protein-enriched corneocytes, and lipid-enriched intercellular domains [1]. The lipids for barrier function are synthesized in the keratinocytes of the nucleated epidermal layers, stored in the lamellar bodies, and extruded into the intercellular spaces during the transition from the stratum granulosum to the SC forming a system of continuous membrane bilayers [1, 2]. In addition to the lipids, other components such as melanins, proteins of the SC and epidermis, free amino acids, and other small molecules also play important roles in the protective barrier of the skin. A list of the different structural as well as functional components of the SC is shown in Table 1.1.

Corneocytes

Corneocytes are formed by the terminal differentiation of the keratinocytes from the granular layer of the epidermis. The epidermis contains 70% water as do most tissues, yet the SC contains only 15% water. Alongside this change in water content the keratinocyte nuclei and virtually all the subcellular organelles begin to disappear in the granular cell layer leaving a proteinaceous core containing keratins, other structural proteins, free amino acids, and amino acid derivatives, and melanin particles that persist throughout the SC. From an oval or polyhedral shape of the viable cells in the spinous layers, the keratinocyte starts to flatten off in the granular cell layer and then assumes a spindle shape and finally becomes a flat corneocyte. The corneocyte itself develops a tough chemically resistant protein band at the periphery of the cell, called cornified cell envelope, formed from cross-linked cytoskeletal proteins [3].

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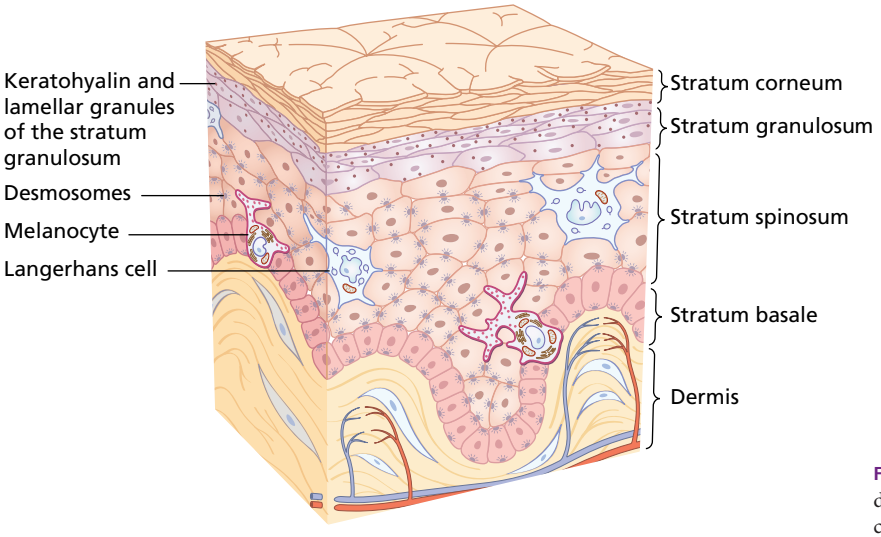

Figure 1.1 Diagram of the epidermis indicating the different layers of the epidermis and other structural components of the epidermal barrier.

Table 1.1 Structural and functional components of the stratum corneum.

Components	Function	Location
Stratum corneum (SC)	Protection	Topmost layer of epidermis
Cornified envelope (CE)	Resiliency of SC	Outer surface of the SC
Cornified envelope precursor proteins	Structural proteins that are cross-linked to form CE	Outer surface of the SC
Lamellar granules (LG)	Permeability barrier of skin	Granular cells of epidermis
SC interfacial lipids	Permeability barrier of skin	Lipid bilayers between SC
Lipid–protein cross-links	Scaffold for corneocytes	Between SC and lipid bilayers
Desmosomes and corneodesmosomes	Intercellular adhesion and provide shear resistance	Between keratinocytes and corneocytes
Keratohyalin granules	Formation of keratin "bundles" and NMF precursor proteins	Stratum granulosum
Natural moisturizing factor (NMF)	Water holding capacity of SC	Within SC
pH and calcium gradients	Provides differentiation signals and LG secretion signals	All through epidermis
Specialized enzymes (lipases, glycosidases, and proteases)	Processing and maturation of SC lipids, desquamation	Within LG and all through epidermis
Melanin granules and "dust"	UV protection of skin	Produced by melanocytes of basal layer, melanin "dust" in SC

Proteins of the cornified envelope

Cornified envelope (CE) contains highly cross-linked proteins formed from special precursor proteins synthesized in the granular cell layer, particularly involucrin, loricrin, and cornifin. In addition to these major protein components, several other minor unique proteins are also cross-linked to the CE. These include proteins with specific functions such as calcium-binding proteins, antimicrobial and immune functional proteins, proteins that provide structural integrity to SC by binding to lipids and desmosomes, and protease inhibitors. The cross-linking is promoted by the enzyme transglutaminase that is detectable histochemically in the granular cell layer and lower segments of the SC. The γ-glutamyl link that results from transglutaminase activity is extremely chemically resistant and this provides the cohesivity and resiliency to the SC.

Lamellar granules and inter-corneocyte lipids

Lamellar granules or bodies (LG or LB) are specialized lipid carrying vesicles formed in suprabasal keratinocytes, destined for delivery of the lipids in the interface between the corneocytes. These lipids form the essential component of the epidermal permeability barrier and provide the "mortar" into which the corneocyte "bricks" are laid for the permeability barrier formation. When the granular keratinocytes mature

to the SC, specific enzymes within the LB process the lipids, releasing the nonpolar epidermal permeability barrier lipids, namely, cholesterol, free fatty acids (FFAs), and ceramides, from their polar precursors-phospholipids, glucosyl ceramides, and cholesteryl sulfate, respectively. These enzymes include lipases, phospholipases, sphingomyelinases, glucosyl ceramidases, and sterol sulfatases [4, 5]. The lipids fuse together in the SC to form a continuous bilayer. It is these lipids along with the corneocytes that constitute the bulk of the water barrier property of the SC [4, 6].

Lipid–protein cross-links at the cornified envelope

LG are enriched in a specific lipid unique to the keratinizing epithelia such as the human epidermis. This lipid (a ceramide) has a very long chain omega-hydroxy fatty acid moiety with linoleic acid linked to the omega hydroxyl group in ester form. This lipid is processed within SC to release the omega hydroxyl ceramide that gets cross-linked to the amino groups of the CE proteins. The molecular structure of these components suggests that the glutamine and serine residues of CE envelope proteins such as loricrin and involucrin are covalently linked to the omega hydroxyl ceramides [6, 7]. In addition, other FFAs and ceramides (Cer), may also form protein cross-links on the extracellular side of the CE, providing the scaffold for the corneocytes to the lipid membrane of the SC.

Desmosomes and corneodesmosomes

Desmosomes are specialized cell structures that provide cell-to-cell adhesion (Figure 1.1). They help to resist shearing forces and are present in simple and stratified squamous epithelia as in human epidermis. Desmosomes are molecular complexes of cell adhesion proteins and linking proteins that attach the cell surface adhesion proteins to intracellular keratin cytoskeletal filaments proteins. Some of the specialized proteins present in desmosomes are cadherins, calcium-binding proteins, desmogleins, and desmocollins. Cross-linking of other additional proteins such as envoplakins and periplakins further stabilizes desmosomes. Corneodesmosomes are remnants of the desmosomal structures that provide the attachment sites between corneocytes and cohesiveness for the corneocytes in the SC. Corneodesmosomes have to be degraded by specialized proteases and glycosidases, mainly serine proteases (SP), for the skin to shed in a process called desquamation [8].

Keratohyalin granules

Keratohyalin granules are irregularly shaped granules present in the granular cells of the epidermis, thus providing these cells the granular appearance (Figure 1.1). These organelles contain abundant amount of keratins "bundled" together by a variety of other proteins, most important of which is filaggrin (**fil**ament **agg**regating prote**in**). An important role of this protein, in addition to bundling of the major structural protein, keratin of the epidermis, is to provide the natural moisturizing factor (NMF) for the SC. Filaggrin contains all the amino acids that are present in the NMF. Filaggrin, under appropriate conditions, is dephosphorylated and proteolytically digested during the process when granular cells mature into corneocytes. The amino acids from filaggrin are further converted to the NMF components by enzymatic processing and are retained inside the corneocytes as components of NMF [4, 9].

Functions of epidermal barrier

Water evaporation barrier (epidermal permeability barrier)

Perhaps the most studied and the most important function of SC is the formation of the epidermal permeability barrier [1, 4, 9]. SC limits the transcutaneous movement of water and electrolytes, a function that is essential for terrestrial survival. Lipids, particularly ceramides, cholesterol, and FFAs, together form lamellar membranes in the extracellular spaces of the SC that limit the loss of water and electrolytes. Corneocytes are embedded in this lipid-enriched matrix, and the CE, which surrounds corneocytes, provides a scaffold necessary for the organization of the lamellar membranes. Extensive research, mainly by Peter Elias' group has elucidated the structure, properties, and the regulation of the skin barrier by integrated mechanisms [5, 10, 11]. Barrier disruption triggers a cascade of biochemical processes leading to rapid repair of the epidermal barrier. These steps include increased keratinocyte proliferation and differentiation, increased production of corneocytes and production, processing and secretion of barrier lipids, ultimately leading to the repair of the epidermal permeability barrier. These events are described in more detail in the barrier homeostasis section below. A list of the different functions of human epidermis is shown in Table 1.2.

Table 1.2 Barrier functions of the epidermis.

Function	Localization/components involved
Water and electrolyte permeability barrier	SC/corneocyte proteins and extracellular lipids
Mechanical barrier	SC/corneocytes, cornified envelope
Microbial barrier/immune function	SC/lipid components/viable epidermis
Hydration/moisturization	SC/NMF
Protection from environmental toxins/drugs	SC/corneocytes, cornified envelope
Desquamation	SC/epidermis/proteases and glycosidases
UV barrier	SC/melanins of SC/epidermis
Oxidative stress barrier	SC, epidermis/antioxidants

Mechanical barrier

CE provides mechanical strength and rigidity to the epidermis, thereby protecting the host from injury. Specialized protein precursors and their modified amino acid cross-links provide the mechanical strength to the SC. One such protein, trichohyalin is a multifunctional cross-bridging protein that forms intra and inter protein cross-links between cell envelope structure and cytoplasmic keratin filament network [12]. Special enzymes called transglutaminases, some present exclusively in the epidermis (transglutaminase 3), catalyze this cross-linking reaction. In addition, adjacent corneocytes are linked by corneodesmosomes, and many of the lipids of the SC barrier are also chemically cross-linked to the CE. All these chemical links provide the mechanical strength and rigidity to the SC.

Antimicrobial barrier and immune protection

The epidermal barrier acts as a physical barrier to pathogenic organisms that attempt to penetrate the skin from the outside environment. Secretions such as sebum and sweat and their acid pH provide antimicrobial properties to skin. Microflora that normally inhabit human skin can contribute to the barrier defenses by competing for nutrients and niches that more pathogenic organisms require, by expressing antimicrobial molecules that kill or inhibit the growth of pathogenic microbes and by modulating the inflammatory response [13]. Desquamation that causes the outward movement of corneocytes and their sloughing off at the surface also serves as a built-in mechanism inhibiting pathogens from colonizing the skin. Innate immune function of keratinocytes and other immune cells of the epidermis such as Langerhans cells and phagocytes provide additional immune protection in skin. Epidermis also generates a spectrum of antimicrobial lipids, peptides, nucleic acids, proteases, and chemical signals that together forms the antimicrobial barrier (Table 1.3). The antimicrobial peptides are comprised of highly conserved small cysteine-rich cationic proteins that are expressed in large amounts in skin. They contain common secondary structures that vary from α helical to β sheets, and their unifying characteristic is the ability to kill microbes or inhibit them from growing. Pathways that generate and regulate the antimicrobial barrier of the skin are closely tied to pathways that modulate the permeability barrier function. Expression of endogenous AMPs coincides with the presence of a number of epidermal structural components that may become part of the permeability barrier. For instance, murine cathelin-related antimicrobial peptide CRAMP and mBD-3 are essential for permeability barrier homeostasis. In addition, acute and chronic skin barrier disruption lead to increased expression of murine β-defensins (mBDs)-1, -3, and -14, and this increase in expression is diminished when the barrier is artificially restored [13].

Table 1.3 Antimicrobial components of epidermis and stratum corneum.

Component	Class of compound	Localization
Free fatty acids	Lipid	Stratum corneum
Glucosyl ceramides	Lipid	Stratum corneum
Ceramides	Lipid	Stratum corneum
Sphingosine	Lipid	Stratum corneum
Defensins	Peptides	Epidermis
Cathelicidin	Peptides	Epidermis
Psoriasin	Protein	Epidermis
RNAse 7	Nucleic acid	Epidermis
Low pH	Protons	Stratum corneum
"Toll-like" receptors	Protein signaling molecules	Epidermis
Proteases	Proteins	Stratum corneum and epidermis

NMF and skin hydration/moisturization

NMF is a collection of water-soluble compounds that are found in the SC (Table 1.4). These compounds compose approximately 20–30% of the dry weight of the corneocyte. Many of the components of the NMF are derived from the hydrolysis of filaggrin, a histidine-, and glutamine-rich basic protein of the keratohyalin granule. SC hydration level controls the protease that hydrolyzes filaggrin and histidase that converts histidine to urocanic acid. As NMF is water soluble and can easily be washed away from SC, the lipid layer surrounding the corneocyte helps seal the corneocyte to prevent loss of NMF.

In addition to preventing water loss from the organism, SC also acts to provide hydration and moisturization to skin. NMF components absorb and hold water allowing the outermost layers of the SC to stay hydrated despite exposure to the harsh external environment. Glycerol, a major component of the NMF, is an important humectant present in skin that contributes skin hydration. Glycerol is produced locally within SC by the hydrolysis of triglycerides by lipases but also taken up into the epidermis from the circulation by specific receptors present in the epidermis called Aquaporins [14]. Other humectants in the NMF include urea, sodium, and potassium lactates and PCA [9].

Table 1.4 Approximate composition of skin natural moisturizing factor.

Components	% levels
Amino acids and their salts (over a dozen)	30–40
Pyrrolidine carboxylic acid (PCA) sodium salt, urocanic acid, ornithine, citrulline (derived from filaggrin hydrolysis products)	7–12
Urea	5–7
Glycerol	4–5
Glucosamine, creatinine, ammonia, uric acid	1–2
Cations (sodium, calcium, potassium)	10–11
Anions (phosphates, chlorides)	6–7
Lactate	10–12
Citrate, formate	0.5–1.0

Protection from environmental toxins and topical drugs penetration

The SC also has the important task of preventing toxic substances and topically applied drugs from penetrating the skin. SC acts as a protective wrap due to the highly resilient and cross-linked protein coat of the corneocytes and the lipid-enriched intercellular domains. Pharmacologists and topical or "transdermal" drug developers are interested in increasing SC permeation of drugs into the skin. The multiple route(s) of penetration of drugs into the skin can be via hair follicles, interfollicular sites, or by penetration through corneocytes and lipid bilayer membranes of the SC. The molecular weight, solubility, and molecular configuration of the toxins and drugs greatly influence the rate of penetration. Different chemical compounds adopt different pathways for skin penetration.

Desquamation and the role of proteolytic enzymes

The process by which individual corneocytes are sloughed off from the top of the SC is called desquamation. Normal desquamation is required to maintain the homeostasis of the epidermis. Corneocyte-to-corneocyte cohesion is controlled by the intercellular lipids as well as the corneodesmosomes that bind the corneocytes together. The presence of specialized proteolytic enzymes and glycosidases in the SC help in cleavage of desmosomal bonds resulting in release of corneocytes [8]. In addition, SC also contains protease inhibitors that keep these proteases in check and the balance of protease – protease inhibitors play a regulatory role in the control of the desquamatory process. The desquamatory process is also highly regulated by the epidermal barrier function.

The SC contains three families of proteases (serine, cysteine, and aspartate proteases), including the epidermal-specific SP, kallikrein-5 (SC tryptic enzyme, SCTE), and kallikrein-7 (SC chymotryptic enzyme), as well as at least two cysteine proteases, including the SC thiol protease (SCTP), and at least one aspartate protease, cathepsin D. All these proteases play specific roles in the desquamatory process at different layers of the epidermis.

Melanin and UV barrier

Although melanin is not typically considered a functional component of epidermal barrier, its role in the protection of the skin from UV radiation is indisputable. Melanins are formed in specialized dendritic cells called melanocytes in the basal layers of the epidermis. The melanin produced is transferred into keratinocytes in the basal and spinous layers. There are two types of melanin, depending on the composition and the color. The darker eumelanin is most protective to UV than the lighter, high sulfur-containing pheomelanin. The keratinocytes carry the melanins through the granular layer and into the SC layer of the epidermis. The melanin "dust" present in the SC is structurally different from the organized melanin granules found in the viable deeper layers of the epidermis. The content and composition of melanins also change in SC depending on sun exposure and skin type of the individual.

Solar ultraviolet radiation is very damaging to proteins, lipids, and nucleic acids and causes oxidative damage to these macromolecules. The SC absorbs some ultraviolet energy but it is the melanin particles inside the corneocytes that provide the most protection. Darker skin (higher eumelanin content) is significantly more resistant to the damaging effects of UV on DNA than lighter skin. In addition, UV-induced apoptosis (cell death that results in removal of damaged cells) is significantly greater in darker skin. This combination of decreased DNA damage and more efficient removal of UV-damaged cells play a critical role in the decreased photocarcinogenesis seen in individuals with darker skin [15]. In addition to melanin, trans-urocanic acid (tUCA), a product of histidine deamination produced in the SC, also acts as an endogenous sunscreen and protects skin from UV damage.

Oxidative stress barrier

The SC has been recognized as the main cutaneous oxidation target of UV and other atmospheric oxidants such as pollutants and cigarette smoke. Depletion of atmospheric "ozone layer" allows most energetic UV wavelength of sun radiation, i.e. UVC and short UVB to reach earth level. This high-energy UV radiation penetrates deep into papillary dermis. UVA radiation in addition to damaging DNA of fibroblasts, also indirectly causes oxidative stress damage of epidermal keratinocytes. The oxidation of lipids and carbonylation of proteins of the SC lead to disruption of epidermal barrier and poor skin condition [16]. In addition to its effects on SC, UV also initiates and activates a complex cascade of biochemical reactions within the epidermis, causing depletion of cellular antioxidants and antioxidant enzymes such as superoxide dismutase (SOD) and catalase. Acute and chronic exposure to UV has been associated with depletion of SOD and catalase in the skin of hairless mice [17]. This lack of antioxidant protection further causes DNA damage, formation of thymine dimers, activation of proinflammatory cytokines and neuroendocrine mediators, leading to inflammation and free radical generation [18]. Skin naturally uses antioxidants to protect itself from photodamage. UV depletes antioxidants from outer SC. A gradient in the antioxidant levels (alpha-tocopherol, vitamin C, glutathione, and urate) with the lowest concentrations in the outer layers and a steep increase in the deeper layers of the SC protects the SC from the oxidative stress [19]. Depletion of antioxidant protection leads to UV-induced barrier abnormalities. Topical application of antioxidants would support these physiological mechanisms and restore a healthy skin barrier [6, 20].

Regulation of barrier homeostasis

Epidermal barrier is constantly challenged by environmental and physiological factors. Since a fully functional epidermal barrier is required for terrestrial life to exist, barrier homeostasis is tightly regulated by a variety of mechanisms.

Desquamation

Integral components of the barrier, corneocytes, and the intercellular lipid bilayers are constantly synthesized and secreted by the keratinocytes during the process of terminal differentiation. Continuous renewal process is balanced by desquamation that removes individual corneocytes in a controlled manner by degradation of desmosomal constituent proteins by the SC proteases. The protease activities are under the control of protease inhibitors that are co-localized with the proteases within the SC. In addition, the activation cascade of the SC proteases is also controlled by the barrier requirement. Lipids and lipid precursors such as cholesterol sulfate also regulate desquamation by controlling the activities of the SC proteases [21].

Corneocyte maturation

Terminal differentiation of keratinocytes to mature corneocytes is controlled by calcium, hormonal factors, and desquamation. High calcium levels in the outer nucleated layers of epidermis stimulate specific protein synthesis and activate the enzymes that induce the formation of corneocytes. Variety of hormones and cytokines control keratinocyte terminal differentiation, thereby regulating barrier formation. Many of the regulators of these hormones are lipids or lipid intermediates that are synthesized by the epidermal keratinocytes for the barrier function, thereby exerting control of barrier homeostasis by affecting the corneocyte maturation. For example, the activators/ligands for the nuclear hormone receptors (example: PPAR – peroxisome proliferation-activated receptor and vitamin D receptor) that influence keratinocyte terminal differentiation are endogenous lipids synthesized by the keratinocytes.

Lipid synthesis

Epidermal lipids, the integral components of the permeability barrier, are synthesized and secreted by the keratinocytes in the stratum granulosum after processing and packaging into the LB. Epidermis is a very active site of lipid synthesis under basal conditions and especially under conditions when the barrier is disrupted. Epidermis synthesizes ceramides, cholesterol, and FFAs (major component of phospholipids and ceramides). These three lipid classes are required in equimolar distribution for proper barrier function. The synthesis, processing, and secretion of these lipid classes are under strict control by the permeability barrier requirements. For example, under conditions of barrier disruption, rapid and immediate secretion by already packaged LB occurs as well as transcriptional and translational increases in key enzymes required for new synthesis of these lipids to take place. In addition, as explained in the previous section, many of the hormonal regulators of corneocyte maturation are lipids or lipid intermediates synthesized by the epidermis. SC lipid synthesis and lipid content are also altered with various skin conditions such as inflammation and winter xerosis [22, 23].

Environmental and physiological factors

Barrier homeostasis is under control of environmental factors such as humidity variations. High humidity (increased SC hydration) downregulates barrier competence (as assessed by barrier recovery after disruption) whereas low humidity enhances barrier homeostasis. Physiological factors can also have influence on barrier function. High stress (chronic as well as acute) increases corticosteroid levels and causes disruption of barrier homeostasis. During periods of psychological stress, the cutaneous homeostatic permeability barrier is disturbed, as is the integrity and protective function of the SC. Many skin diseases, including atopic dermatitis and psoriasis, are precipitated or exacerbated by psychological stress [24]. Circadian rhythmicity also applies to skin variables related to skin barrier function. Significant circadian rhythmicity has been observed in transepidermal water loss (TEWL), skin surface pH, and skin temperature. These observations suggest skin permeability is higher in the evening than in the morning [25]. Conditions that cause skin inflammation can stimulate the secretion of inflammatory cytokines such as interleukins, induce epidermal hyperplasia, cause impaired differentiation and disrupt epidermal barrier functions.

Skin conditions and disease states

Epidermal lipid profiles and barrier architecture are altered in many common skin conditions. Atopic dermatitis, or eczema, is associated with significantly lower levels of ceramides with abnormal lipid organization, reduced barrier function, and skin hydration [26, 27]. Table 1.5 summarizes the changes in SC lipid composition and barrier function associated with common pathological skin conditions. The abnormal lipid profile and

Table 1.5. Changes in stratum corneum lipid composition and barrier function associated with common skin conditions.

Skin condition	Change in SC lipid composition	Effect of skin barrier function
Atopic dermatitis [26, 27]	Decreased total ceramide level	Reduced barrier function and hydration
Psoriasis [28, 29]	Decreased total ceramide levels in lesional skin compared to nonlesional skin Severity of psoriatic lesions correlated with a reduction in ceramide synthesis	Reduced barrier function and hydration
Acne vulgaris [30]	Reduced total ceramides	Reduced barrier function
Keratosis pilaris [31]	No change to lipid composition reported Disrupted epidermal lipid bilayers	Reduced barrier function

impaired barrier function contribute to the clinical symptoms of xerosis, disordered desquamation, and pruritus typical associated with eczema and psoriasis.

Neonates

Skin developments start *in utero* during the first trimester, with a well-defined SC appearing around 34 gestational weeks [32]. At birth, skin is covered in a hydrophobic biofilm called the vernix caseosa. The vernix layer forms during the third trimester and can be thought of as a "mobile phase" SC, composed of sebaceous and epidermal lipids combined with desquamating of maturing fetal corneocytes (~80% water, ~10% protein, and ~10% lipids). The vernix serves a protective role for the fetus and neonate, thought to assist with water loss, temperature regulation, acid mantle formation, and antimicrobial and antioxidant defenses [33, 34]. Infant skin is not fully mature at birth; its structure, composition, and function continues developing after birth and continues through the first years of life [32] (Table 1.6).

Physiological differences in infant skin reflect a developing barrier. This can leave children in a vulnerable state, which could be associated with the proneness for children to develop pathological conditions, such as atopic dermatitis. In recent years, several studies have explored the prophylactic use of emollients in reducing the incidence of atopic dermatitis in "high risk" infants, defined as those with a parent or full sibling with physician-diagnosed atopic dermatitis, asthma, or allergic rhinitis. In a pilot study with 124 newborns in the United States and the United Kingdom, daily emollient application versus typical infant care without emollient application found a reduced cumulative incidence of atopic dermatitis (relative risk reduction of 50%) for the treatment group after six months [35].

Table 1.6. Summary of infant skin structure, composition, and function in comparison to normal adult skin [32].

	Infant skin compared to adult skin
Skin structure	
Corneocyte size	Smaller
Stratum corneum thickness	30% thinner
Dermal structure	Flatter dermal papillae No distinction between papillary and reticular dermis
Skin composition	
Water content	Drier at birth
NMF concentration	Lower
Surface lipid concentration	Lower
Melanin concentration	Lower
Skin function	
Barrier function/TEWL	Lower at birth
pH	Higher
Cell proliferation rate	Higher

Source: Data from Stamatas et al. 2011 [*Int J Cosmetic Sci*, **33**, 17–24.].

Aging

Skin aging is characterized by profound functional changes. In the epidermis, these include reduced capacities for protection against mechanical and chemical insults, maintenance of hydration and osmotic balance, immunological defense, and toxin elimination [36]. While there are multifactorial etiologies for these changes, age-related deterioration of the skin barrier is a primary cause. Skin barrier abnormalities can be attributed, in large part, to reduced delivery of secreted lipids to the SC, and a resultant decrease in the number of extracellular lamellar bilayers it contains [37, 38]. Although these bilayers are healthy and intact, the extracellular matrix may be more permeable in aged than in the young epidermis. If aged skin becomes dehydrated or damaged, its dysfunction may be exacerbated and the barrier more easily compromised. Studies of TEWL demonstrate that the barrier of aged skin recovers significantly more slowly than young skin after damage from repeated tape stripping [37].

Hormones

Barrier homeostasis/SC integrity, lipid synthesis is all under the control of different hormones, cytokines, and calcium. Nuclear hormone receptors for both well-known ligands, such as thyroid hormones, retinoic acid, and vitamin D, and "liporeceptors" whose ligands are endogenous lipids control barrier homeostasis. These liporeceptors include peroxisome proliferator activator receptor (PPAR alpha, beta, and gamma) and liver X receptor (LXR). The activators for these receptors are endogenous lipids and lipid intermediates or metabolites such as certain FFAs, leukotrienes, prostanoids, and oxygenated sterols. These hormones mediated by their receptors control barrier at the level of epidermal cell maturation (corneocyte formation), transcriptional regulation of terminal differentiation proteins, and enzymes required for lipid processing, lipid transport and secretion into LB.

pH and calcium

Outermost SC pH is maintained in the acidic range, typically in the range of 4.5–5.0 by a variety of different mechanisms. This acidity is maintained by formation of FFAs from phospholipids; sodium proton exchangers in the SC and by the conversion of histidine of the NMF to urocanic acid by histidase enzyme in the SC**.** In addition, lactic acid, a major component of the NMF, plays a major role in maintaining the acid pH of the SC. Maintenance of an acidic pH in the SC is important for the integrity/cohesion of the SC as well as the maintenance of the normal skin microflora. The growth of normal skin microflora is supported by acidic pH while a more neutral pH supports pathogenic microbes' invasion of the skin.

This acidic pH is optimal for processing of precursor lipids to mature barrier-forming lipids and for initiating the

desquamatory process. The desquamatory proteases present in the outer SC such as the thiol proteases and cathepsins are more active in the acidic pH, whereas the SCCE and SCTE present in the lower SC are more active at the neutral pH. Under conditions when the pH gradient is disrupted, desquamation is decreased resulting in dry scaly skin and disrupted barrier function.

In the normal epidermis, there is a characteristic intraepidermal calcium gradient, with peak concentrations of calcium in the granular layer and decreasing all the way up to the SC [39]. The calcium gradient regulates barrier properties by controlling the maturation of the corneocytes, regulating the enzymes that process lipids, and modulating the desquamatory process. Calcium stimulates a variety of processes including the formation and secretion of lamellar bodies, differentiation of keratinocytes, formation of CE precursor proteins, and cross-linking of these proteins by the calcium inducible enzyme transglutaminase. Specifically, high levels of calcium stimulate the expression of proteins required for keratinocyte differentiation, including key structural proteins of the CE, such as loricrin, involucrin, and the enzyme, transglutaminase 1, which catalyzes the cross-linking of these proteins into a rigid structure.

Coordinated regulation of multiple barrier functions

Co-localization of many of the barrier functions allows regulation of the functions of the epidermal barrier to be coordinated. For example, epidermal permeability barrier, antimicrobial barrier, mechanical protective barrier, and UV barrier are all co-localized in the SC. A disruption of one function can lead to multiple barrier disruptions, and therefore, multiple barrier functions are coordinately regulated. Disruption of permeability barrier leads to activation of cytokine cascade (increased levels of primary cytokines, interleukin-1, and tumor necrosis factor-alpha) which in turn activates the synthesis of antimicrobial peptides of the SC. In addition, the cytokines and growth factors released during barrier disruption lead to corneocyte maturation thereby strengthening the mechanical and protective barrier of the skin. Hydration of the skin itself controls barrier function by regulating the activities of the desquamatory proteases (high humidity decreases barrier function and stimulates desquamation). In addition, humidity levels control filaggrin hydrolysis that release the free amino acids that form the NMF (histidine, glutamine arginine, and their byproducts) and tUCA (deamination of histidine) that serves as UV barrier.

Methods for studying barrier structure and function

Physical methods

SC integrity/desquamation can be measured using tape stripping methods. Under dry skin conditions, when barrier is compromised, corneocytes do not separate singly but as "clumps." This can be quantified by using special tapes and visualizing the corneocytes removed by light microscopy. Another harsher tape-stripping method involves stripping of SC using cyanoacrylate glue. These physical methods provide a clue to the binding forces that hold the corneocyte together. The efficacy of treatment with skin moisturizers or emollients that improve skin hydration and reduce scaling can be quantitated using these methods.

Instrumental methods

The flux of water vapor through the skin (transepidermal water loss or TEWL) can be determined using an evaporimeter [40]. This instrument contains two water sensors mounted vertically in a chamber one above the other. When placed on the skin in a stable ambient environment the difference in water vapor values between the two sensors is a measure of the flow of water coming from the skin (TEWL). There are several commercially available evaporimeters [e.g. Tewameter® Courage & Khazaka (Köln, Germany)], which are widely used in clinical practice as well as in investigative skin biology. Recovery of epidermal barrier (TEWL) after barrier disruption using physical methods (e.g. tape strips) or chemical methods (organic solvent washing) provides valuable information on the epidermal barrier properties [41].

Skin hydration can be measured using Corneometer®. The measurement is based on capacitance of a dielectric medium. Any change in the dielectric constant due to skin surface hydration variation alters the capacitance of a precision measuring capacitor. The measurement can detect even slightest changes in the hydration level. Another important recent development in skin capacitance methodology is using SkinChip®. Skin capacitance imaging of skin surface can be obtained using SkinChip. This method provides information regarding skin microrelief, level of SC hydration, and sweat gland activity. SkinChip technology can be used to quantify regional variation in skin, skin changes with age, effects of hydrating formulations, surfactant effects on corneocytes, acne, and skin pore characteristics [42].

Several other recently developed methods for measuring epidermal thickness such as confocal microscopy, dermatoechography, and dermatoscopy can provide valuable information on skin morphology and barrier abnormalities [43]. Other more sophisticated (although not easily portable) instrumentation techniques such as ultrasound, optical coherence tomography, and the magnetic resonance imaging (MRI) can provide useful information on internal structures of SC/epidermis and its improvements with treatment. MRI has been successfully used to evaluate skin hydration and water behavior in aging skin [44].

Biological methods

Ultrastructural details of SC and the intercellular spaces of the SC can be visualized using transmission electron microscopy (TEM) of thin vertical sections and freeze-fracture replicas, field emission scanning electron microscopy (SEM), and

immunofluorescence confocal laser scanning microscopy [45]. The ultrastructural details of the lipid bilayers within the SC can be visualized by EM after fixation using ruthenium tetroxide. The existence of corneodesmosomes in the SC and their importance in desquamation can be measured by scanning electron microscopy (SEM) of skin surface replicas.

The constituent cells of the SC, the corneocytes, can be visualized and quantitated by scraping the skin surface or by use of detergent solution. The suspension so obtained can be analyzed by microscopy, biochemical, or immunological techniques.

Punch or shaved biopsy techniques can be combined with immunohistochemistry using specific SC/epidermis-specific antibodies to quantify the SC quality. Specific antibodies for keratinocyte differentiation-specific proteins, desmosomal proteins, or specific proteases can provide answers relating to skin barrier properties.

Relevance of skin barrier to cosmetic product development

Topical products that influence barrier functions

The human skin is constantly exposed to hostile environment. These include changes in relative humidity, extremes of temperature, environmental toxins, and daily topically applied products. Daily exposure to soaps and other household chemicals can compromise skin barrier properties and cause unhealthy skin conditions. Allergic reactions to topical products can result in allergic or irritant contact dermatitis, resulting in itchy and, scaly skin and skin redness leading to barrier perturbations.

In particular, cleansing products including alkaline soaps and synthetic detergents are associated with the disruption of the skin barrier. Soaps, the alkaline salts of fatty acids, leave the skin dry and feeling tight. This is attributed to their high pH and protein binding leading to swelling and hyperhydration that quickly evaporates leaving behind a dehydrated and damaged barrier. In addition to efficiently cleaning the skin's surface, soaps also remove NMF epidermal lipids, damaging the skin barrier. Synthetic surfactants typically have a lower pH and range in degree of harshness. Surfactants have the potential to bind to and denature proteins and remove both NMF and lipids like soaps; however, they are a diverse class of ingredient and the degree to which a synthetic surfactant disrupts the barrier is associated to its properties such as charge density and pH [46, 47].

Cosmetics that restore skin barrier properties

Water is the most important plasticizer of SC. Cracking and fissuring of skin develop as SC hydration declines below a critical threshold. Skin moisturization is a property of the outer SC (also known as stratum disjunctum) as corneocytes of the lower SC (stratum compactum) are hydrated by the body fluids. "Moisturizers" are substances that when applied to skin add water and/or retains water in the SC. Moisturizers affect the SC architecture and barrier homeostasis, that is, topically applied ingredients are not as inert to the skin as one might expect. A number of different mechanisms behind the barrier-influencing effects of moisturizers have been suggested, such as simple deposition of lipid material outside the skin. Ingredients in the moisturizers may also change the lamellar organization and the packing of the lipid matrix and thereby change skin permeability [48]. The NMF components present in the outer SC act as humectants, absorb moisture from the atmosphere, and are sensitive to humidity of the atmosphere. The amino acids and their metabolites, along with other inorganic and organic osmolytes such as urea, lactic acid, taurine, and glycerol act as humectants within the outer SC. Secretions from sebaceous glands on the surface of the skin also act as emollients and contribute to skin hydration. A lack of either or any of these components can contribute to dry, scaly skin. Topical application of all of the above components can act as humectants, and can relieve dry skin condition, and improve skin moisturization and barrier properties. Film-forming polysaccharide materials such as hyaluronic acid, binds, and retains water and helps to keep skin supple and soft.

In addition to humectants, emollients such as petroleum jelly, hydrocarbon oils and waxes, mineral and silicone oils and paraffin wax provide an occlusive barrier to the skin, preventing excessive moisture loss from the skin surface.

Topically applied barrier compatible lipids also contribute to skin moisturization and improved skin conditions. Chronologically aged skin exhibits delayed recovery rates after defined barrier insults, with decreased epidermal lipid synthesis. Application of a mixture of cholesterol, ceramides, and essential/non-essential FFAs in an equimolar ratio was shown to lead to normal barrier recovery, and a 3 : 1 : 1 : 1 ratio of these four ingredients demonstrated accelerated barrier recovery [49]. A novel, cholesterol-dominant topical formulation containing high concentrations of ceramides (2%), natural cholesterol (4%), and omega fatty acids (2%) has established its ability to improve barrier function and specific indices of skin aging. This novel cholesterol-dominant physiological lipid formulation demonstrated significant improvements in clinical signs of aging including skin tone and texture, radiance, clarity, fine lines and wrinkles, firmness, laxity, appearance of pores, and global appearance [50]. Lipid analysis showed that the same formulation induced significant increases in the epidermal content of total ceramides, cholesterol, and triglycerides after eight weeks of treatment. Furthermore, in a clinical model of skin barrier repair, where the formula was applied for one week prior to skin injury by tape stripping, skin treated with the formulation achieved significantly more rapid and greater recovery of barrier function than untreated skin [50].

A complementary approach is the topical application of ingredients that stimulate the de novo synthesis of epidermal lipids. The daily application of nicotinamide, also called niacinamide, increased the level of ceramides and FFAs in skin and improved skin's water barrier [51]. Topical application of antioxidants and

anti-inflammatory agents also protects skin from UV-induced skin damage by providing protection from oxidative damage to skin proteins and lipids [6, 20].

Topically applied substances may penetrate deeper into the skin and interfere with the production of barrier lipids and the maturation of corneocytes. Creams may influence the desquamatory proteases and change the thickness of the SC. The increased understanding of the interactions between topically applied substances and epidermal biochemistry will enhance the possibilities to tailor skin care products for various SC abnormalities [48].

Skin irritation from cosmetics

Thousands of ingredients are used by the cosmetic industry. These include pure compounds, mixtures, plant extracts, oils and waxes, surfactants, detergents, preservatives, and polymers. Although all the ingredients used by the cosmetic industry are tested for safety, some consumers may still experience reactions to some of them. Most common reactions are irritant contact reactions while allergic contact reactions are less common. Irritant reactions tend to be more rapid and cause mild discomfort and redness and scaling of skin. Allergic reactions can be delayed, more persistent, and sometimes severe. Ingredients previously considered safe can be irritating in a different formulation because of increased skin penetration into skin. More than 50% of the general population perceives their skin as sensitive. It is believed that the perception of sensitive skin is at least in part, related to skin barrier function. People with impaired barrier function may experience higher irritation to a particular ingredient due to its increased penetration into deeper layers of the skin.

Summary and future trends

Major advances have been made in the last several decades in understanding the complexity and functions of the SC. Extensive research by several groups has elucidated the metabolically active role of the SC and has characterized the major components and their importance in providing protection for the organism from the external environment. New insights into the molecular control mechanisms of desquamation, lipid processing, barrier function, and antimicrobial protection have been elucidated in the last decade.

Knowledge of other less well-known epithelial organelles such as intercellular junctions, tight junctions, and gap junctions and their role in barrier function in the skin is being elucidated. Intermolecular links that connect intercellular lipids with the corneocytes of the SC and their crucial role for maintaining barrier function are an area being actively researched.

New knowledge in the corneocyte envelope structure and the physical state of the intercellular lipid crystallinity and their interrelationship would lead to development of new lipid actives for improving SC moisturization and for treatment of skin barrier disorders. Further research in the cellular signaling events that control the communication between SC and the viable epidermis will shed more light into barrier homeostasis mechanisms.

Novel delivery systems play an increasingly important role in the development of effective skin care products. Delivery technologies such as lipid systems, nanoparticles, microcapsules, polymers, and films are being pursued not only as vehicles for delivering cosmetic actives through skin but also for improving barrier properties of the skin.

Interest and research on the relationship between skin conditions and barrier functions are expected to grow, as existing and ongoing research suggests the barrier to be a relevant therapeutic target for helping to address the symptoms, and potentially the development, of pathological skin conditions.

Undoubtedly, skin care and cosmetic companies will exploit this new knowledge in developing novel and more efficacious products for strengthening the epidermal barrier and to improve and enhance the functional and aesthetic properties of the human skin.

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CHAPTER 2

Photoaging

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BASIC CONCEPTS

- The normal dermal matrix is maintained through signaling transduction pathways, transcription factors, cell surface receptors, and enzymatic reactions.
- Ultraviolet (UV) radiation damages human skin connective tissue through several interdependent, but distinct, processes.
- UV radiation produces reactive oxygen species, which inhibit procollagen production, degrade collagen, and damage fibroblasts.
- Prevention of photoaging with sun protection is more efficacious and affordable than managing clinical signs of photoaging once they have developed.

Introduction

Skin, the largest human organ, is chronically exposed to UV radiation from the sun. The skin is at the frontline of defense for the human body against the harmful effects of UV exposure. Chronic absorption of UV radiation leads to photoaging, sunburn, immunosuppression, and carcinogenesis. Photoaging is the most common form of skin damage caused by UV exposure, affecting connective tissue, melanocytes, and the microvasculature [1]. Recent advances in understanding photoaging in human skin have identified the physical manifestations, histologic characteristics, and molecular mechanisms of UV-induced skin damage.

Definition

Photoaging describes the clinical, histologic, and functional changes that occur in the skin as a result of long-term exposure to UV radiation. Chronic UV exposure results in premature or accelerated skin aging, which is marked clinically by fine and coarse wrinkling of the skin, dyspigmentation, sallow color, textural changes, loss of elasticity, and premalignant actinic keratoses. Most of these clinical signs are caused by dermal alterations. Pigmentary disorders such as seborrheic keratoses, lentigines, and diffuse hyperpigmentation are characteristic of epidermal changes [2]. The clinical features of photoaged skin are superimposed on changes seen with intrinsic chronological aging of the skin.

These clinical characteristics are confirmed histologically by epidermal thinning and disorganization of the dermal connective tissue. Solar elastosis, caused by the accumulation of disorganized connective tissue elastin, is a characteristic histologic finding of photoaged skin [3]. Similar alterations seen in the cellular component and the extracellular matrix of connective tissue may affect superficial capillaries, causing surface telangiectasias clinically [4].

The significance of photoaging lies in both the cosmetic and medical repercussions – in the demand for agents that can prevent or reverse the cutaneous signs associated with photoaging and its strong association with cutaneous malignancies. In 2017, the global anti-aging product market was estimated to be US$324.6 billion and is expected to reach US$429 billion by 2022 [5]. Furthermore, UV-induced cutaneous malignancies, namely basal cell carcinoma and squamous cell carcinoma, are the most common malignancies diagnosed in the United States, with approximately 5.4 million cases diagnosed annually [6].

Clinical features

Physical characteristics of photoaged versus chronologically aged skin

Skin ages over time like all other organs. Skin aging can be subdivided into intrinsic and extrinsic aging. Intrinsic aging is a hallmark of human chronological aging and occurs in both sun-exposed and sun-protected skin. Extrinsic aging, on the contrary, is affected by exposure to environmental factors such

Cosmetic Dermatology: Products and Procedures, Third Edition. Edited by Zoe Diana Draelos.

as UV radiation. While sun-protected chronologically aged skin and photoaged chronologically aged skin share common characteristics, many of the physical qualities of skin that decline with age show an accelerated decline with photoaging [7]. Chronologically aged skin is characterized by dryness, fine wrinkles, skin atrophy, homogeneous pigmentation, and seborrheic keratoses [8]. Extrinsically aged skin, on the contrary, is characterized by roughness, dryness, fine as well as coarse wrinkles, atrophy, uneven pigmentation, and superficial vascular abnormalities (telangiectasias) [8]. It is important to note that these attributes are not absolute and can vary according to Fitzpatrick skin type classification and history of sun exposure.

Histology of photoaged versus chronologically aged skin

While the pathophysiology of photoaged and chronologically aged skin overlap, the histologic features of these two entities are distinct. In chronologically aged skin, the epidermis is thin with an intact stratum corneum, the dermoepidermal junction and the dermis are flattened, and dermal fibroblasts produce less collagen. In photoaged skin, the thickness of the epidermis can either increase or decrease, corresponding to areas of keratinocyte atypia. The dermoepidermal junction is atrophied in appearance and the basement membrane thickness is increased, reflecting basal keratinocyte damage.

Changes in the dermis of photoaged skin can vary based on the amount of acquired UV damage. Solar elastosis is the most prominent histologic feature of photoaged skin. While the quantity of elastin in the dermis decreases in chronologically aged skin, it increases in proportion to the amount of UV exposure in photoaged skin [9, 10]. Accumulated elastic fibers occupy areas in the dermal compartment previously inhabited by collagen fibers [11]. This altered elastin deposition, or solar elastosis, is seen clinically as wrinkles and yellow discoloration of the skin.

Another feature of photoaged skin is collagen fibril disorganization. Mature collagen fibers, which constitute the bulk of the skin's connective tissue, are replaced by collagen with a basophilic appearance, termed basophilic degeneration. Additional histologic characteristics of photoaged skin include an increase in the deposition of glycosaminoglycans and dermal extracellular matrix proteins [12, 13]. In fact, the overall cell population in photodamaged skin increases, leading to hyperplastic fibroblast proliferation and infiltration of inflammatory substrates that cause chronic inflammation, or heliodermatitis [14]. Changes in the microvasculature also occur, as is clinically manifested in surface telangiectasias and other vascular abnormalities.

Cutaneous vasculature in chronologically aged skin and photoaged skin share similar characteristics, such as decreased cutaneous temperature, pallor, decreased cutaneous vessel size, reduced erythema, reduced cutaneous nutritional supply, and reduced cutaneous vascular responsiveness [15–17]. However, there are also significant differences in the microvasculature. Studies have reported that the blood vessels in photoaged skin are obliterated and the overall horizontal architecture of the vascular plexuses is disrupted [18]. In contrast to photodamaged skin, chronologically aged skin does not display a greatly disturbed pattern of horizontal vasculature. In addition, while cutaneous vessel size has been reported to decrease with age in both, only photoaged skin exhibits a large reduction in the number of dermal vessels. This reduction is especially highlighted in the upper dermal connective tissue, where it is hypothesized that the chronic UV-induced degradation of elastic and collagen fibers limits the ability to provide the physical support required for normal cutaneous vessel maintenance [15].

The effects to skin vasculature may differ between acute and chronic UV exposure. Recent studies have implied that a single exposure to UVB radiation induces skin angiogenesis in human skin *in vivo* [19, 20]. The epidermis-derived vascular endothelial growth factor (VEGF) is an angiogenic factor that is significantly upregulated with UV exposure in keratinocytes *in vitro* and in human skin *in vivo*. Chung and Eun [15] demonstrated that epidermal VEGF expression increased significantly on days 2 and 3 post-UV-irradiation compared to non-UV-irradiated control skin, consequently inducing cutaneous angiogenesis. Therefore, acute UV exposure induces angiogenesis. In contrast, chronic UV-exposed photodamaged skin is known to have a significant reduction in the number of cutaneous blood vessels. The reason for this discrepancy is still under investigation.

Photoaging in ethnic skin

All races are susceptible to photoaging. However, people with Fitzpatrick skin phototypes IV–VI are less susceptible to the deleterious effects of UV irradiation than people with a lower Fitzpatrick skin type classification. This phenomenon is most likely a result of the protective role of melanin [21]. Studies reporting characteristics of photoaging in ethnic skin are limited and findings are briefly highlighted. Hopefully, as new scales for assessing photoaging in ethnic skin are established and validated, research in this area will increase [22].

Kaidbey *et al.* [23] compared UV absorption of African-American skin with Caucasian skin. It is known that only 10% of the total UVB rays penetrates the dermis. However, the mean UVB transmission into the dermis of African-American skin was found to be significantly less than in Caucasian dermis (5.7% vs. 29.4%, respectively). Similar experiments were performed with UVA irradiation. UVA transmission into African-American dermis was 17.5% compared to 55% for Caucasian epidermis [23]. The physiologic reason behind this difference in black and white skin lies at the site of UV filtration. The malpighian layer (basal cell layer) of African-American skin is the main site of UV filtration, while the stratum corneum absorbs most UV rays in Caucasian skin. The malpighian layer of African-American skin removes twice as much UVB radiation as the overlying stratum corneum, thus mitigating the deleterious effects of UV rays in the underlying dermis [24].

Langton *et al.* [25] characterized the biomechanical and histologic characteristics of photoaging in African-American skin. Skin exposed to chronic UV demonstrated reduced biomechanical properties, such as elasticity, over and above that observed in chronologically aged skin. Histology of skin samples showed that photoaging resulted in complete flattening of the dermoepidermal junction, disruption of elastin fiber organization, and remodeling of the collagen fibrillar matrix. Notably, solar elastosis, a characteristic histologic finding of photoaging in fair skin-types, was not detected [25].

In African-Americans, photoaging may not be clinically apparent until the fifth or sixth decade of life and is more common in individuals with a lighter complexion [26]. The features of photoaging in this ethnic skin group manifest as signs of laxity in the malar fat pads sagging toward the nasolabial folds, as well as dermatosis papulosa nigra [27, 28]. In patients of Hispanic and European descent, photoaging occurs in the same frequency as Caucasians and clinical signs are primarily wrinkling rather than pigmentary alterations. On the contrary, skin of East and South-East Asian patients mainly exhibits pigmentary alterations (seborrheic keratoses, hyperpigmentation, actinic lentigines, sun-induced melasma) as a result of photoaging. Wrinkling is minimal and occurs later in life [28–30]. Finally, very few studies have reported on the signs of photoaging in South Asian (Pakistani, Indian) skin. UV-induced hyperpigmentation, dermatosis papulosa nigra, and seborrheic keratosis are noted [31].

It is important to note that the number of melanocytes per unit area of skin does not vary across ethnicities. Instead, it is the relative amount of melanin packaged into melanocytes that accounts for the pigmentation differences between Caucasian skin and ethnic skin [32]. Increasing age leads to senescence of melanocytes; senescent melanocytes, in turn, can cause greater melanin production that has been observed in some darker-skinned individuals [33]. This may be responsible for the general "bronzing," and darkening, appearing as a "permanent tan" observed in some photoaged individuals of darker skin tones. A recent study, however, observed that pigmentation decreased with age in sun-exposed sites compared to sun-protected sites in African Americans. This pattern was opposite in Caucasian study participants, where sun-exposed sites were darker than sun-protected sites [34].

Genetics of photoaging

Genetics may also play a role in photoaging. A recent meta-analysis of five genome-wide association studies from three different cohorts identified genetic alleles that may affect the severity of skin aging. The authors found that single-nucleotide polymorphisms (SNP) near the SLC45A2, IRF4, and MC1R genes were significantly associated with wrinkling and photoaging. Interestingly, the lower-pigmentation alleles of each gene were associated with more severe photoaging mirroring the established association between low-pigmentation alleles and the increased risk of melanoma and keratinocyte carcinomas [35].

Molecular mechanisms of photoaging

Substantial progress has been made to ascertain the molecular mechanisms accountable for photoaging in human skin. UV irradiation damages human skin by at least three interdependent mechanisms:

1. Direct damage to DNA
2. Photochemical generation of reactive oxygen species (ROS)
3. Activation of signal transduction pathways leading to downstream effects on cutaneous connective tissue and vasculature

Gene expression profiles from Caucasian females ranging in age from 20 to nearly 75 years old revealed age-induced and photoinduced changes in pathways related to oxidative stress, senescence, metabolism, and barrier function. Molecular patterns of gene expression in women that were younger appearing were similar to women that were actually younger [36]. The prominent molecular processes of photoaging are described in detail below. Before these processes are highlighted, however, it is important to consider the biology of UV radiation as well as the structure and function of collagen, which plays a key role in the strength and integrity of the skin.

Photobiology

The UV spectrum is further categorized into three subtypes: UVC (270–290 nanometers [nm]), UVB (290–320 nm), and UVA (320–400 nm). UVC radiation is filtered by the ozone layer and atmospheric moisture, and consequently never reaches the Earth. In contrast, UVA and UVB rays do reach the terrestrial surface; the ratio of UVA to UVB rays is 20:1 [37] and UVB is greatest during the summer months. Both forms of radiation have acute and chronic effects on human skin.

In order to exert biologic effects on human skin, both categories of UV rays must be absorbed by chromophores in the skin. UV light interacts with different skin cells at different depths depending on the wavelength absorbed (Figure 2.1). More specifically, energy from UVB rays is mostly absorbed by the epidermis and affects epidermal cells such as the keratinocytes, whereas energy from UVA penetrates deeper into the skin, affecting both epidermal keratinocytes and the deeper dermal fibroblasts. Approximately 50% of UVA penetrates the skin in a fair-skinned individual (versus <10% of UVB photons). The absorbed energy is converted into varying chemical reactions that cause histologic and clinical changes in the skin. UVA absorption by chromophores mostly acts indirectly by transferring energy to oxygen to generate ROS, leading to transcription factor activation, lipid peroxidation, and DNA-strand breaks. On the contrary, UVB has a more direct effect on the absorbing chromophores by damaging DNA via cross-linking of adjacent DNA pyrimidines, among other mechanisms [39]. Up to 50% of UV-induced photodamage is from the formation of free radicals, while mechanisms such as direct cellular injury account for the remainder of UV effects [40]. Thus UVB induced photodamage is implicated as the predominant cause of photoaging.

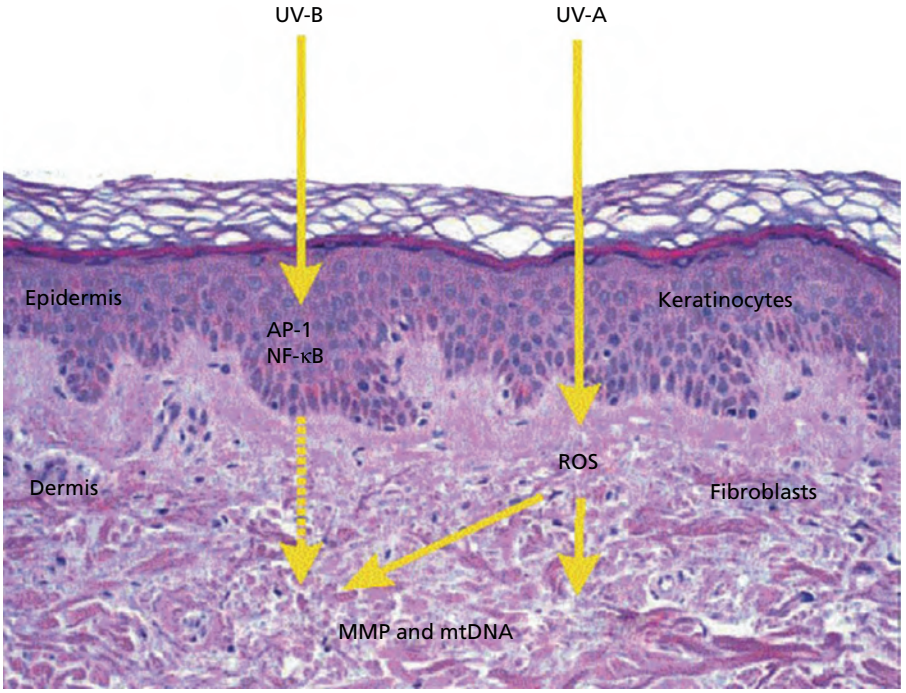

Figure 2.1 Ultraviolet light interacts with different skin cells at different depths. More specifically, energy from UVB rays is mostly absorbed by the epidermis and affects epidermal cells such as the keratinocytes. Energy from UVA rays affects both epidermal keratinocytes and the deeper dermal fibroblasts. AP-1, activator protein 1; NF-κB, nuclear factor κB; MMP, matrix metalloproteinase; mtDNA, mitochondrial DNA; ROS, reactive oxygen species. (Source: Berneburg *et al.*, 2000 [38]. Reproduced with permission of John Wiley & Sons.)

The important role of UVA in photoaging, however, stems from the fact that in distinction to UVB, UVA is also transmitted through glass. This enables exposure while indoors, near windows, as well as while driving leading to significant long-term exposure. Evidence for this includes dramatic unilateral dermatoheliosis in some long-term occupational drivers [41].

Collagen

The unique physical characteristics of collagen fibers are essential for providing strength, structural integrity, and resilience to the skin. Type I collagen accounts for greater than 90% of the protein in the human skin, with type III collagen accounting for a smaller fraction (10%). Dermal fibroblasts synthesize individual collagen polypeptide chains as precursor molecules called procollagen. These procollagen building blocks are assembled into larger collagen fibers through enzymatic cross-linking and form the three-dimensional dermal network. This intermolecular covalent cross-linking step is essential for maintenance and structural integrity of large collagen fibers, especially type I collagen.

Collagen gene expression in human skin fibroblasts is regulated by the cytokine transforming growth factor β (TGF-β) and the transcription factor activator protein (AP-1). When TGF-βs bind to its cell surface receptors (TβRI and TβRII), transcription factors Smad2 and Smad3 are activated, combine with Smad4, and enter the nucleus, where they regulate type I procollagen production. AP-1 has an opposing effect and inhibits collagen gene transcription by either direct suppression of gene transcription or obstructing the Smad complex from binding to the TGF-β target gene (Figure 2.2) [42]. Therefore, in the absence of any inhibiting factors, the TGF-β/Smad signaling pathway results in a net increase in procollagen production.

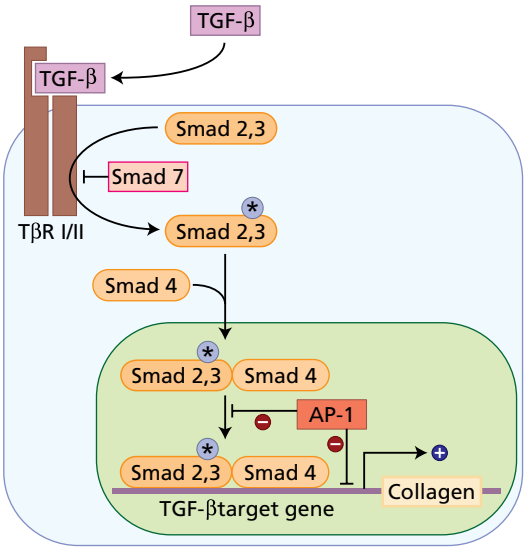

Figure 2.2 The regulation of procollagen production: the TGF-β/Smad signaling pathway. AP-1, activator protein 1; TβR, TGF-β receptor; TGF-β, transforming growth factor β. (Source: Kang *et al.*, 2001 [3]. Reproduced with permission of Elsevier.)

The natural breakdown of type I collagen is a slow process and occurs through enzymatic degradation [43]. Dermal collagen has a half-life of greater than 1 year [43]. This slow rate of type I collagen turnover allows for disorganization and fragmentation of collagen that impair its functions. Fragmentation and dispersion of collagen fibers are features of photodamaged skin.

How does UV irradiation stimulate photoaging?

UV irradiation stimulates photoaging through several molecular mechanisms, discussed in detail below.

UVB leads to direct DNA damage

DNA damage and defective DNA repair mechanisms have been implicated in carcinogenesis as well as the intrinsic aging process [44]. Mechanisms of photoaging similarly feature DNA damage. UVB radiation directly damages DNA by promoting the formation of thymine–thymine dimers (most frequently cyclobutane pyrimidine dimers) and pyrimidine pyrimidone photoproducts (namely 6-4 photoproduct). Thymine–thymine dimers may cause mutations in the tumor suppressor gene p53 leading to photoaged skin, actinic keratosis, and skin cancer. DNA repair mechanisms may also be affected by UV radiation. A recent study showed that UVA impaired the repair of cyclobutane dimers induced by UVB [45].

Reactive oxygen species

Proposed in 1954, the free radical theory of aging suggests that aging is a result of reactions caused by excessive amounts of free radicals, which contain one or more unpaired electrons [46]. Generation of ROS occurs during normal chronological aging as well as in response to UV light exposure in photoaging [47]. There are two main pathways of ROS formation in the skin. The first involves the creation of entities such as superoxide anion, peroxide, and singlet oxygen that are formed with UV exposure. Their levels normalize once exposure ends. In the second pathway, activated nicotinamide adenine dinucleotide phosphate catalyzes a reaction between molecular oxygen and superoxide anion to create the ROS hydrogen peroxide [48]. ROS mediate deleterious posttranslational effects on aging skin through direct chemical modifications to DNA, mitochondrial DNA (mtDNA), cell lipids, and dermal matrix proteins, including collagens. In fact, a marker of UVA-induced photodamage via ROS is a 4977 base-pair deletion of mtDNA in human dermal fibroblasts [49].

The role of ROS in photoaging is not limited to UVA. UVB enhances the levels of NF-κB responsive proteins, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and induces the production of nitric oxide (NO). NO is a central player in the regulation of skin cell apoptosis. Furthermore, upon reacting with ROS, NO is transformed into cytotoxic peroxynitrite ($ONOO^-$) which causes lipid peroxidation. Lipid peroxidants are, in part, responsible for the wrinkle formation that is a hallmark of photoaging [50].

UV radiation inhibits procollagen production: TGF-β/Smad signaling pathway

UV light inhibits procollagen production through two signaling pathways: downregulation of TGF-β type II receptor (TβRII) resulting in reduced signaling of the TGF-β/Smad pathway and inhibition of target gene transcription by AP-1 [1]. UV radiation downregulates the TβRII and results in a 90% reduction of TGF-β cell surface binding, consequently reducing downstream activation of the Smad 2, 3, 4 complex and ultimately transcription of type I procollagen.

In addition, UV radiation activates AP-1, which binds factors that are part of the procollagen type I transcriptional complex. This, in turn, reduces TGF-β target gene expression and the formation of type I procollagen [51].

UV-induced matrix metalloproteinases stimulate collagen degradation

UVA and UVB light induces a wide variety of matrix metalloproteinases (MMP) [38]. As their name suggests, MMPs degrade dermal matrix proteins, specifically collagens, through enzymatic activity. UV-induced MMP-1 cleaves type I and III collagen, that is further degraded by MMP-3 and MMP-9.

Recall that type I collagen fibrils are stabilized by covalent cross-links. When undergoing degradation by MMPs, collagen molecules can remain cross-linked within the dermal collagen matrix, impairing the structural integrity of the dermis. In the absence of perfect repair mechanisms, MMP-mediated collagen damage can accrue with each UV exposure. This type of cumulative damage to the dermal matrix collagen is hypothesized to have a direct effect on the physical characteristics of photodamaged skin [39].

In addition to UV induction of MMPs directly, UV-activated transcription factors may cause MMP activation. It has been reported that within hours of UV exposure, the transcription factors AP-1 and NF-κB are activated and, in turn, stimulate transcription of MMPs [52].

Fibroblasts regulate their own collagen synthesis

Fibroblasts have evolved to regulate their output of extracellular matrix proteins (including collagen) based on internal mechanical tension [53]. Type I collagen fibrils in the dermis serve as mechanical stabilizers and attachment sites for fibroblasts in sun-protected skin. Surface integrins on the fibroblasts attach to collagen and internal actin–myosin microfilaments provide mechanical resistance by pulling on the intact collagen. In response to this created tension, intracellular scaffolding composed of intermediate filaments and microtubules pushes outward to causing fibroblasts to stretch. This stretch is an essential cue for normal collagen and MMP production by fibroblasts [53].

This mechanical tension model is different in photoaged human skin. Fibroblast–integrin attachments are lost, which prevents collagen fragments from binding to fibroblasts. Collagen–fibroblast binding is crucial for maintenance of normal mechanical stability. When mechanical tension is reduced, as in

photoaged skin, fibroblasts collapse, which causes decreased procollagen production and increased collagenase (COLase) production [53]. Collagen is continually lost as this cycle repeats itself.

Elastosis and cathepsins

One of the histologic hallmarks of photoaging is elastolysis and an accumulation of abnormal elastin in the superficial dermis known as solar elastosis. One of the most potent enzymes involved in the degradation of elastin is cathepsin K [54]. This enzyme is induced in young fibroblasts in response to UVA irradiation and leads to digestion and clearance of extracellular elastin. This induction was not seen in fibroblasts from old donors [55]. Thus, cathepsin K appears to play a critical part in clearing MMP-digested elastin in the ECM, a function which is lost with age and leads to the histologic (and corresponding clinical effects) of elastosis [44]. Other studies have also demonstrated the downregulation of cathepsins B, D, and K and upregulation of cathepsin G in photoaged skin and senescent fibroblasts *in vitro* [56].

UVA induces the aging-associated progerin

Recent data have implicated a protein called progerin as a mechanism of UV-induced aging. Patients with Hutchinson–Gilford progeria syndrome (HGPS) have a mutation in LMNA, which encodes an abnormal and truncated form of Lamin A, called progerin [57]. Accumulation of progerin has been shown to result in misshapen nuclei with disrupted nuclear functions, including reduced DNA repair capacity, increased telomere shortening, and increased activation of p53, which ultimately result in a reduced cellular lifespan due to early senescence [58–64].

Progerin has been reported to contribute to aging not only of HPGS cells but also of normal cells. There is an accumulation of progerin-expressing cells in skin with increasing age [21].

Hirotaka Takeuchi and Thomas M. Rünger recently showed that UVA induces progerin expression in cultured primary human fibroblasts, particularly in aged cells obtained from older donors. These cells had subsequent abnormal nuclear shapes and presumably abnormal nuclear functions, suggesting a novel mechanism by which UV light accelerates aging of the skin [63].

Prevention

Although the effects of the sun's rays appear daunting, there are several ways to avoid the deleterious effects of photoaging. Preventing photoaging is more effective and affordable than attempting to reverse the signs of photoaging after they have manifested.

Primary prevention

Sun protection

UV rays are especially prevalent during the hours of 10 am–4 pm and sun protection should be especially encouraged during this time. Sun protection can be offered to patients in the form of sunscreen, sun-protective clothing, and/or sun avoidance. Sun-protective clothing includes any hats, sunglasses, or clothing that would help block the sun's rays. Photoprotective clothing is given a UV protection factor (UPF) rating, which is a measurement of the amount of irradiation that can be transmitted through a specific type of fabric. Most dermatologists recommend a UPF of 40–50, as it transmits less than 2.6% of UV irradiation [7].

Sunscreens reflect, scatter, or absorb photons of UV light. Sunscreen ingredients are categorized as either mineral or chemical. Mineral sunblocks contain the inorganic particulates titanium dioxide or zinc oxide that protect by reflecting both UVA and UVB radiation. Chemical sunscreens, such as those that contain avobenzone, oxybenzone, octocrylene (among others), absorb UVA radiation. When combined with physical blockers, chemical sunscreens can provide broad-spectrum UV protection [65]. The recommended dose of sunscreen application is 2 mg/cm^2 [66]. The US Food and Drug Administration (FDA) is currently reviewing safety of chemical sunscreen ingredients and issued a proposed rule in 2019 to update the regulatory requirements for over-the-counter sunscreen. Two recent studies found evidence of systemic absorption of common sunscreen ingredients with both single application and maximal recommend application [66, 67]. The health risks of sunscreen absorption have not yet been established, and regular sunscreen use is still recommended [65].

Sunscreen efficacy is measured by sun protection factor (SPF). The SPF can range from 1 to over 80 and indicates the time that a person can be exposed to UVB rays before getting sunburned with sunscreen application relative to the time a person can be exposed without sunscreen. SPF levels are determined by the minimal amount of UV irradiation that can cause UVB-stimulated erythema and/or pain. The effectiveness of a particular sunscreen depends on several factors, including the initial amount applied, amount reapplied, user skin type, amount of sunscreen the skin has absorbed, and the activities of the user (e.g. swimming, sweating).

The SPF is an inadequate determination of skin damage because it does not account for UVA rays. Although UVA rays have an important role in photoaging, their effects are not physically evident as erythema or pain, as are UVB rays. Therefore, it has been suggested that SPF may be an imperfect guide to the ability of a particular sunscreen to shield against photoaging [7]. As a result, combination broad-spectrum sunscreens have been developed and are recommended to protect the human skin from both types of irradiation.

An Australian study investigated the effects of daily use of sunscreen (with or without β-carotene supplementation) and found that consistent use of sunscreen had a significant effect on photoaging relative to a matched group of individuals with discretionary sunscreen usage [68]. Thus, individuals should be encouraged to use daily broad-spectrum sunscreen in adequate quantity and frequency of application to gain benefit from the photoprotective effects of these agents. The authors saw no effect on aging with β-carotene use, however, power was limited.

Secondary prevention

Retinoids

Retinoids exert their effects by binding to two groups of receptors belonging to the nuclear receptor superfamily: the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). Activation of RARs and RXRs, in turn, results in molecular changes, which favor collagen deposition and increasing epidermal thickness.

Specifically, all-*trans* retinoic acid (ATRA) has been shown to induce type I and III procollagen gene expression in photoaged skin [69]. It has been observed that topical ATRA induces TGF-β in human skin [70], which stimulates the production of type I and III procollagen.

In addition, ATRA has been used in a preventive fashion to avert UV-induced angiogenesis. Kim *et al.* [19] demonstrated that topical application of retinoic acid before UV exposure inhibited UV-induced angiogenesis and increases in blood vessel density. In general, extracellular signal-related kinases (ERKs, or classic MAP kinases) positively regulate epidermally derived VEGF. VEGF stimulates angiogenesis upon UV induction. Retinoic acid inhibits ERKs, which can potentially lead to down-regulation of VEGF expression, UV-induced angiogenesis, and angiogenesis-associated photoaging (Figures 2.3 and 2.4) [15].

Finally, ATRA has been reported to prevent UV-stimulated MMP expression. Recall that the AP-1 complex both inhibits types I and III procollagen and stimulates transcription of MMPs. Retinoic acid blocks the accumulation of c-Jun protein, consequently inhibiting the formation of the AP-1 complex and thus preventing dermal matrix-associated degradation by MMPs [71].

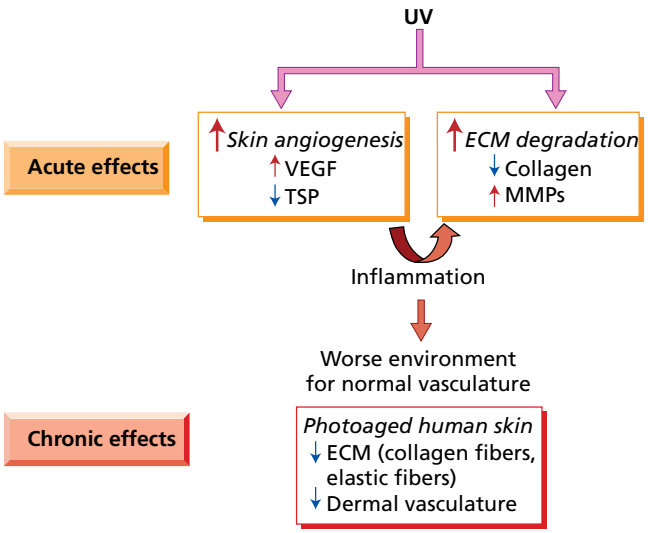

Figure 2.3 Model depicting the acute and chronic effects of UV irradiation on skin angiogenesis and extracellular matrix (ECM) degradation in human skin. MMP, matrix metalloproteinase; TSP, thrombospondin-1 (ECM protein; inhibitor of angiogenesis in epithelial tissues); VEGF, vascular endothelial growth factor. (Source: Chung and Eun, 2007 [15]. Reproduced with permission of John Wiley & Sons.)

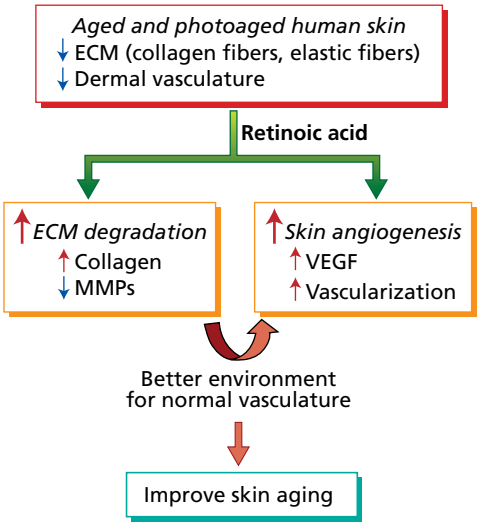

Figure 2.4 Model depicting the effect of topical retinoids on photoaged human skin. ECM, extracellular matrix; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor. (Source: Chung and Eun, 2007 [15]. Reproduced with permission of John Wiley & Sons.)

Clinically, retinoids have been used to prevent photoaging and reverse the signs of photodamage. Tretinoin and tazarotene are two topical retinoids that are FDA approved for the treatment of photoaging. Both have been shown to reduce fine wrinkles, dyspigmentation, and skin surface roughness in clinical trials [72–76]. Adapalene, a retinoid available over-the-counter, is not FDA approved for photoaging but has demonstrated efficacy [77–79]. In contrast to topical retinoids, limited data exist in support of the use of oral retinoids for photoaging [80–82].

Antioxidants

It is important to briefly highlight the role of antioxidants in the prevention of photoaging. *In vitro* studies have discovered a large number of antioxidants that either forestall or reverse the clinical signs of photodamage caused by ROS. Vitamin C has been shown to mitigate photodamaged keratinocyte formation and erythema post-UV-irradiation [83]. Evidence exists indicating benefit of vitamin C, vitamin B3 (nicotinamide), and vitamin E in the treatment and prevention of photoaging [84]. Effects of other antioxidants on human skin fibroblasts have also been studied, including green tea polyphenols (GTPs), caffeine (mostly in combination with GTP), and resveratrol (a phytoalexin, a naturally occurring compound derived from plants). These have been shown to inhibit the generation of free radicals in human skin fibroblasts *in vitro* [85, 86]. Oral supplementation with lycopene and lutein products demonstrated decreased expression of genes associated with UV oxidative stress [87]. However, the effects of antioxidants remain controversial as numerous studies have evaluated the effects of a variety of antioxidants on photoaging with variable effectiveness and *in vitro* studies do not necessarily equate to clinical improvement in randomized controlled clinical trials [84, 88–91].

Inherent defense mechanisms

Though science has developed exogenous mechanisms to prevent and reverse the clinical signs of photoaging, the human skin possesses powerful endogenous machinery built to protect the skin from UV-induced damage. These inherent defense mechanisms include, but are not limited to, increased epidermal thickness, melanin distribution, DNA repair mechanisms, apoptosis of sunburned keratinocytes, MMP tissue inhibitors, and antioxidants [7, 23, 92–94].

Conclusions

The pathophysiology of photoaging stems from the ability of UV irradiation to exploit established molecular mechanisms that have evolved to maintain the internal milieu of human skin connective tissue. Disruption of the normal skin architecture does not occur through one pathway, but rather is the culmination of several interdependent, but distinct processes. The integrity of the normal dermal matrix is maintained through signaling transduction pathways, transcription factors, cell surface receptors, and enzymatic reactions that are overlap and communicate with one another. When UV irradiation is introduced into this homeostasis, deleterious effects ensue. Production of ROS, inhibition of procollagen production, collagen degradation, and fibroblast collapse are only a few known processes amongst the medley of mechanisms still waiting to be discovered that contribute to photoaging. Although human skin is equipped with inherent mechanisms to protect against photoaging and methods of prevention and therapeutics are widely available, these alternatives are not absolute and do not necessarily guarantee complete protection from the sun's UV irradiation. Consumer demand for agents capable of preventing or improving the stigmata of photoaging, association of photoaging with malignancies of the skin, as well as insights gained into the process of aging overall provide stimulus to scientists for the continuous study and discovery of pathways involved in extrinsic aging. Novel cutaneous molecular mechanisms affected by UV irradiation are being discovered, and consequently, research is underway to discover new solutions to photodamage.

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CHAPTER 3

Pigmentation and Skin of Color

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BASIC CONCEPTS

- Differences in the structure, function, and physiology of the hair and skin in individuals of skin of color are important in understanding the structural and physiologic variations that exist and influence disease presentations.
- Melanin, the major determinant of skin color, absorbs UV light and blocks free radical generation, protecting the skin from sun damage and aging.
- UV irradiation of keratinocytes induces pigmentation by the upregulation of melanogenic enzymes, DNA damage that induces melanogenesis, increased melanosome transfer to keratinocytes, and increased melanocyte dendricity.
- Racial differences in hair include the hair type, shape, and bulb.

Introduction

The demographics of the United States reflect a dynamic mixture of people of various ethnic and racial groups. According to the 2010 census, just over one-third of the US population reported their ethnicity and race as something other than non-Hispanic white [1]. Projections of the size and composition of the US Population: 2014 to 2060 noted that by the year 2044, more than half of all Americans will belong to a minority group [2].

Persons of skin of color include Africans, African-Americans, Afro-Caribbeans, Asians, Latinos (Hispanics), Native Americans, Middle Easterners, Alaskan natives, pacific islanders, native Hawaiians, and Mediterraneans. The term "black" as in black skin refers to individuals with African ancestry, including Africans, African-Americans, and Afro-Caribbeans. Subgroups exist within each ethnoracial group. The differences in the structure, function, and physiology of the hair and skin in individuals of skin of color are important in understanding the structural and physiologic variations that exist and influence disease presentations. Pigmentation is especially important in patients of skin of color because pigmentary disorder is the most common reason for a visit to a dermatologist in this group [3].

Melanocytes

Melanin, the major determinant of skin color, absorbs UV light and blocks free radical generation, protecting the skin from sun damage and aging. Melanocytes, the cells that produce melanin, synthesize melanin in special organelles, melanosomes. Melanin-filled melanosomes are transferred from one melanocyte to 30–35 adjacent keratinocytes in the basal layer [4]. The number of melanocytes also decreases with age.

There is more than one type of melanin: eumelanin, a dark brown–black pigment; and pheomelanin, a yellow–reddish pigment. Eumelanin is deposited in ellipsoidal melanosomes which contain a fibrillar internal structure. Synthesis of eumelanin increases after UV exposure (tanning). Pheomelanin has a higher sulfur content than eumelanin because of the sulfur-containing amino acid cysteine. Pheomelanin is synthesized in spherical melanosomes and is associated with microvesicles [5]. Although not obvious to the naked eye, most melanin pigments of the hair, skin and, eyes are combinations of eumelanin and pheomelanin [6]. It is generally believed that genetics determine the constitutive levels of pheomelanin and eumelanin. Eumelanin is more important in determining the degree of pigmentation than pheomelanin. Eumelanin, and not pheomelanin, increases with visual pigmentation [6]. Lighter melanocytes have higher pheomelanin content than dark melanocytes. In one study [6], white persons had the least amount of eumelanin, Asian Indians had more, and African-Americans had the highest. Of note, adult melanocytes contain significantly more pheomelanin than cultured neonatal melanocytes.

Melanosomes also differ among different races. In black persons, they are mostly in the basal layer, but those of white persons are mostly in the stratum corneum. This is evident in the site of UV filtration: the basal and spinous layers in blacks and the stratum corneum in white persons. Of note, the epidermis

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of black skin rarely shows atrophied areas [7]. In black skin, melanocytes contain more than 200 melanosomes. The melanosomes are 0.5–0.8 mm in diameter, do not have a limiting membrane, are stuck closely together, and are individually distributed throughout the epidermis. In white skin, the melanocytes contain less than 20 melanosomes. The melanosomes are 0.3–0.5 mm in diameter, associated with a limiting membrane, and distributed in clusters with spaces between them. The melanosomes of lighter skin degrade faster than that of dark skin. As a result, there is less melanin content in the upper layers of the stratum corneum. Thus, the melanocytes in black skin are larger, more active in making melanin, and the melanosomes are packaged, distributed, and broken down differently than in white skin. Melanosome pH is also another factor that plays a role in regulating differences in skin color. Melanosomes derived from darker skin have a more neutral pH compared to those from lighter skin where the pH is more acidic. Tyrosinase activity is enhanced at neutral pH, thus those with lighter skin have lower tyrosinase activity [8].

There is also a difference in melanosomes between individuals within the same race with varying degrees of pigmentation. Despite greater melanin content in darker skins, there is no evidence of major differences in the number of melanocytes [9]. Also, dark Caucasian skin resembles the melanosome distribution observed in black skin [10]. Black persons with dark skin have large, nonaggregated melanosomes and those with lighter skin have a combination of large nonaggregated and smaller aggregated melanosomes [11]. White persons with darker skin have nonaggregated melanosomes when exposed to sunlight and white persons with lighter skin have aggregated melanosomes when not exposed to sunlight [9, 10, 12]. It has also been shown that the number of melanosomes transferred to keratinocytes is significantly higher in skin of African descent versus white skin [13].

The steps of melanogenesis are as follows. The enzyme tyrosinase hydroxylates tyrosine to dihydroxyphenylalanine (DOPA) and oxidizes DOPA to dopaquinone. Dopaquinone then undergoes one of two pathways. If dopaquinone binds to cysteine, the oxidation of cysteinyldopa produces pheomelanin. In the absence of cysteine, dopaquinone spontaneously converts to dopachrome. Dopachrome is then decarboxylated or tautomerized to eventually yield eumelanin. Melanosomal P-protein is involved in the acidification of the melanosome in melanogenesis [14]. Finally, the tyrosinase activity (not simply the amount of the tyrosinase protein) and cysteine concentration determine the eumelanin–pheomelanin content [6].

Tyrosinase and tyrosinase-related proteins 1 and 2 (TRP-1 and TRP-2) are upregulated when α-melanocyte-stimulating hormone (α-MSH) or adrenocorticotropin binds to melanocortin-1 receptor (MC1R), a transmembrane receptor located on melanocytes [14–17]. The MC1R loss-of-function mutation increases sensitivity to UV-induced DNA damage. Gene expression of tyrosinase is similar between black and white persons despite tyrosinase activity being significantly higher in darker versus lighter skin, but other related genes are expressed differently. The expression of RAB27A, encoding for the melanosome transport molecule, plays an important role in melanocyte melanin content as evident in Griscelli syndrome. In a study by Yoshida-Amano *et al.,* darkly pigmented melanocytes were found to have a substantially higher RAB27A expression and thus able to transfer more to keratinocytes. It was concluded that RAB27A is essential in determining ethnic skin color differences [13]. The MSH cell surface receptor gene for melanosomal P-protein is expressed differently between races. This gene may regulate tyrosinase, TRP-1, and TRP-2 [6].

In addition to the MC1R, protease-activated receptor 2 (PAR-2) is another important receptor that regulates epidermal cells and affects pigmentation [18]. PAR-2 is expressed on many cells and several different organs. Accordingly, the receptor is involved in several physiologic processes, including growth and development, mitogenesis, injury responses, and cutaneous pigmentation. In the skin, PAR-2 is expressed in the keratinocytes of the basal, spinous, and granular layers of the epidermis, endothelial cells, hair follicles, myoepithelial cells of sweat glands, and dermal dendritic-like cells [19, 20]. PAR-2 is a seven-transmembrane domain G-protein-coupled receptor which undergoes activation via proteolytic cleavage of the NH2 terminus which acts as a tethered ligand which then activates the receptor (autoactivation).

Protease-activated receptor 2-activating protease (PAR-2-AP), endothelial cell-released trypsin, mast cell-released trypsin and chymase, and SLIGKV (Ser-Leu-Ile-Gly-Lys-Val) all irreversibly activate PAR-2 while serine protease inhibitors interfere with the activation of the receptor [21–23]. SLIGKV and trypsin activate PAR-2 to use a Rho-dependent signaling pathway to induce melanosomal phagocytosis by keratinocytes. The result is an increase in pigmentation to the same degree as UV radiation [20–24]. Serine proteases are regulatory proteins involved in tumor growth, inflammation, tissue repair, and apoptosis in various tissues [19]. In the skin, serine protease inhibitors prevent the keratinocytes from phagocytosing melanosomes from the presenting dendritic tip of the melanocyte. This leads to a dose-dependent depigmentation without irritation or adverse events.

PAR-2 also has a pro-inflammatory effect in the skin [20]. The activation of PAR-2 expressed on endothelial cells by tryptase, trypsin, or PAR-2-AP leads to an increase in proinflammatory cytokines interleukin 6 (IL-6) and IL-8 and also stimulates NF-κB, an intracellular proinflammatory regulator [21]. Mast cells interact with endothelial cells to regulate inflammatory responses, angiogenesis, and wound healing, and PAR-2 has a regulatory role in this cell–cell interaction [20, 21].

UV irradiation of keratinocytes induces pigmentation in several ways: upregulation of melanogenic enzymes, DNA damage that induces melanogenesis, increased melanosome transfer to keratinocytes, and increased melanocyte dendricity. UV radiation (UVR) increases the secretion of proteases by keratinocytes in a dose-dependent manner. Specifically, UVR directly increases the expression of PAR-2 *de novo*, upregulates proteases that activate PAR-2, and activates dermal mast cell degranulation [24].

According to the literature, PAR-2 expression is different in skin of color compared to white skin thus, suggesting the involvement of PAR-2 in ethnic skin color phenotypes. One study demonstrated that PAR-2 and its activator trypsin are expressed in higher levels in darker skin. PAR-2 was also found to have higher cleavage ability in highly pigmented skin [25].

Another study did find differences in skin phototypes I, II, and III [24]. UVR increases the expression of PAR-2 in the skin and activated PAR-2 stimulates pigmentation. This study found that the response of PAR-2 to UVR is an important determinant of one's ability to tan. In the nonirradiated skin, PAR-2 expression was confined to the basal layer and just above the basal layer. Irradiated skin showed de novo PAR-2 expression in the entire epidermis or upper two-thirds of the epidermis. Skin phototype I had a delayed upregulation of PAR-2 expression compared to phototypes II and III.

Dyspigmentation

After cutaneous trauma or inflammation, melanocytes can react with normal, increased, or decreased melanin production; all of which are normal biologic responses. Increased and decreased production results in postinflammatory hyperpigmentation (PIH) or hypopigmentation. PIH is an increase in melanin production and/or an abnormal distribution of melanin resulting from inflammatory cutaneous disorders or irritation from topical medications [26, 27]. Examples include acne, allergic contact dermatitis, lichen planus, bullous pemphigoid, herpes zoster, and treatment with topical retinoids. Often, the PIH resulting from acne is more distressing to darker-skinned individuals than the initial acute lesion. The color of the hyperpigmentation in PIH depends on the location of the melanin. Melanin in the epidermis appears brown, while melanin in the dermis appears blue–gray. Wood's lamp examination distinguishes the location of the melanin: the epidermal component is enhanced and the dermal component becomes unapparent [27]. Postinflammatory hypopigmentation shares the same triggers as PIH but instead results from decreased melanin production with clinically apparent light areas [26]. The Wood's lamp examination does not accentuate hypopigmentation in postinflammatory hypopigmentation; it is useful for depigmented disorders such as vitiligo and piebaldism.

The pathogenesis of PIH and postinflammatory hypopigmentation are unknown. It is likely that an inflammatory process in the skin stimulates keratinocytes, melanocytes, and inflammatory cells to release cytokines and inflammatory mediators that lead to the hyperpigmentation or hypopigmentation. The cytokines and inflammatory mediators include leukotriene (LT), prostaglandins (PG), and thromboxane (TXB) [28]. Specifically for PIH, *in vitro* studies revealed that LT-C4, LT-D4, PG-E2, and TXB-2 stimulate human melanocyte enlargement and dendrocyte proliferation. LT-C4 also increases tyrosinase activity and mitogenic activity of melanocytes. Transforming growth factor-α and LT-C4 stimulate movement of melanocytes. The basal layer can also be damaged due to inflammation which results in leakage of melanin from keratinocytes and thus accumulation of melanophages in the dermis exacerbating dermal hyperpigmentation [29]. In postinflammatory hypopigmentation, the pathogenesis likely involves inflammatory mediators inducing melanocyte cell-surface expression of intercellular adhesion molecule 1 (ICAM-1) which may lead to leukocyte–melanocyte attachments that inadvertently destroy melanocytes. These inflammatory mediators include interferon-gamma, tumor necrosis factor α (TNF-α), TNF-β, IL-6, and IL-7.

Natural sun protective factor in skin of color

It is clear that those who fall within Fitzpatrick skin phototypes IV–VI are less susceptible to photoaging; this is most likely due to the photoprotective role of melanin [29, 30]. The epidermis of black skin has a protective factor (PF) for UVB of 13.4 and that of white skin is 3.4 [31]. The mean UVB transmission by black epidermis is 5.7% compared to 29.4% for white epidermis. The PF for UVA in black epidermis is 5.7 and in white epidermis is 1.8 [31]. The mean UVA transmission by black epidermis is 17.5% and 55.5% for white epidermis. Hence, 3–4 times more UVA reaches the upper dermis of white persons than that of black persons.

The main site of UV filtration in white skin is the stratum corneum, whereas in black skin it is the basal layer [31]. The Malpighian layer of black skin removes twice as much UVB radiation as the stratum corneum [32]. It is possible that even greater removal of UVA occurs in black skin basal layers [32]. While the above characteristics of natural sun PF were studied in black skin, they can probably be extrapolated to most persons of skin phototypes IV–VI.

Skin of color

Epidermis

The epidermal layer of skin is made up of five different layers: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. The stratum basale (also termed the basal layer) is the germinative layer of the epidermis. The time required for a cell to transition from the basal layer through the other epidermal layers to the stratum corneum is 24–40 days. The morphology and structure of the epidermis are very similar among different races, although a few differences do exist.

Stratum corneum

The stratum corneum, the most superficial layer, is the layer responsible for preventing water loss and providing mechanical protection. The cells of the stratum corneum, the corneocytes,

are flat cells measuring 50 μm across and 1 μm thick. The corneocytes are arranged in layers; the number of layers varies with anatomic site and race. There are no differences between races in corneocyte surface area, which has a mean size of 900 μm [3, 33]. The stratum corneum of black skin is more compact than that of white skin. While the mean thickness of the stratum corneum is the same in black and white skin, black skin contains 20 cell layers while white skin contains 16. The answer to whether or not there are racial differences in spontaneous desquamation is inconclusive [32–34]. It was observed in a study by Wesley and Maibach [35] that blacks have a 2.5 times greater spontaneous desquamation compared with whites and Asians [36]. Parameters for skin barrier function (stratum corneum hydration, sebum secretion, erythema, and laser Doppler flowmetry) are similar, even after an objective epicutaneous test with sodium lauryl sulfate [35].

Transepidermal water loss

Transepidermal water loss (TEWL) is the amount of water vapor loss from the skin, excluding sweat. TEWL increases with the temperature of the skin. Concrete evidence regarding the difference in TEWL between different races has yet to be established. In most studies, TEWL has been found to be greater in black skin compared to white skin but the opposite has also been reported. A study reported no difference in TEWL amongst blacks, whites, and Hispanics [36]. In a more recent study, basal TEWL was evaluated using an Aquaflux AF200 on 30 predefined regions of the face in sixteen South African females of different ethnicities (Indian, Black African, Chinese, and Caucasian). Baseline data were also measured on the volar forearms and dorsal hands. The authors found that TEWL was statistically significantly lower on the volar forearm for the Caucasian patients in comparison to Black African and Indian patients and, on the hands only, lower compared to the Indians. Facial TEWL was found to be similar between the Caucasian and Black African groups with both being lower than the Indian group [37].

Aside from TEWL, hydration is also a characteristic of skin. One of the ways to measure hydration, or water content, is conductance. Conductance, the opposite of resistance, is increased in hydrated skin because hydrated skin is more sensitive to the electrical field [38]. Skin conductance is higher in black persons and Hispanics than white persons [38]. Lipid content in black skin is higher than that of white skin [39]. However, black skin is more prone to dryness, suggesting that a difference in lipid content has a role. This includes the ratio of ceramide : cholesterol : fatty acids, the type of ceramides, and the type of sphingosine backbone. The total levels of ceramides were approximately 50% lower in the stratum corneum of blacks when compared to whites and Hispanics according to a study [40]. One study suggests that the degree of pigmentation influences lipid differences [41].

Pigmentation affects skin dryness. Skin dryness is greater on sun-exposed (dorsal arm) sites for lighter skin, such as Caucasian and Chinese skin, than sites that are primarily out of the sun (ventral arm) [42]. There is no difference in skin dryness between sites for darker skin, such as African-Americans and Mexicans. For adults less than 51 years of age, skin dryness does not change as a function of ethnicity (African-American, Caucasian, Chinese, and Mexican) for sun-exposed sites and sites that are not primarily sun-exposed. For those 51 years of age and older, skin dryness is higher for African-Americans and Caucasians than for Chinese and Mexicans. As a function of age, skin dryness in African-American skin increases 4% on the dorsal site and 3% on the ventral site; in Caucasian skin, it increases 11% on the dorsal site and 10% on the ventral site. All of the above findings suggest that sun exposure can dry the skin and that melanin provides protection.

Skin reactivity

Mast cells

Sueki *et al.* [43] studied the mast cells of four African-American men and four white men (mean age 29 years) by evaluating punch biopsies of the buttocks with electron microscopy, with the following results. The mast cells of black skin contained larger granules (the authors attributed this to the fusion of granules). Black skin also had 15% more parallel-linear striations and 30% less curved lamellae in mast cells. Tryptase reactivity was localized preferentially over the parallel-linear striations and partially over the dark amorphous subregions within granules of mast cells from black skin, whereas it was confined to the peripheral area of granules, including curved lamellae, in white skin. Cathepsin G reactivity was more intense over the electron-dense amorphous areas in both groups, while parallel-linear striations in black skin and curved lamellae in white skin were negative.

Patch test antigens

Contact dermatitis

Irritant contact dermatitis (ICD) is the most common form of dermatitis and loosely defined as nonspecific damage to the skin after exposure to an irritant. The various clinical manifestations are influenced by the concentration of chemicals, duration of exposure, temperature, humidity, and anatomic location, and other factors. Acute contact dermatitis presents with the classic findings of localized superficial erythema, edema, and chemosis. Cumulative contact dermatitis presents with similar findings, but with repeated exposure of a less potent irritant [44].

The susceptibility to ICD differs between black and white skin [45]. The structural differences in stratum corneum of black skin (e.g. compact stratum corneum, low ceramide levels) are credited with decreasing the susceptibility to irritants. Reflectance confocal microscopy (RCM) is an imaging tool that permits real-time qualitative and quantitative study of human skin; when used with a near-infrared laser beam, one can create "virtual sections" of live tissue with high resolution, almost comparable with routine histology. Measuring skin reactivity to chemical irritants with RCM and TEWL reveals that white

skin had more severe clinical reactions than black skin. The pigmentation in darker skin can make the assessment of erythema difficult and interfere with identification of subclinical degrees of irritancy. Even without clinical evidence of irritation, RCM and histology reveal parakeratosis, spongiosis, perivascular inflammatory infiltrate, and microvesicle formation. Mean TEWL after exposure to irritants is greater for white skin than for black skin. This supports the concept that the stratum corneum of black skin enhances barrier function and resistance to irritants.

There are no differences between white persons and African-Americans in objective and subjective parameters of skin such as dryness, inflammation, overall irritation, burning, stinging, and itching [46]. Acute contact dermatitis with exudation, vesiculation, or frank bullae formation is a more common reaction in white skin whereas dyspigmentation and lichenification is more common in black skin [47].

The response to irritation in Caucasian and African-American skin differs in the degree of severity. Caucasian skin has a lower threshold for cutaneous irritation than African-American skin [48]. Caucasian skin also has more severe stratum corneum disruption, parakeratosis, and detached corneocytes. Both groups have the same degree of intra-epidermal spongiosis epidermal (granular and spinous layer) vesicle formation. The variability in human skin irritation responses sometimes creates difficulty in assessing the differences in skin reactivity between human subpopulations. There are conflicting results in studies comparing the sensitivity to irritants in Asian skin with that in Caucasian skin [35, 49–52].

Dermis

The dermis lies deep to the epidermis and is divided into two layers: the papillary and reticular dermis. The papillary dermis is tightly connected to the epidermis via the basement membrane at the dermoepidermal junction. The papillary dermis extends into the epidermis with finger-like projections, hence the name "papillary." The reticular dermis is a relatively avascular, dense, collagenous structure that also contains elastic tissue and glycosaminoglycans. The dermis is made up of collagen fibers, elastic fibers, and an interfibrillar gel of glycosaminoglycans, salt, and water. Collagen makes up 77% of the fat-free dry weight of skin and provides tensile strength. Collagen types I, II, V, and VI are found in the dermis. The elastic fiber network is interwoven between the collagen bundles.

There are differences between the dermis of white and black skin. The dermis of white skin is thinner and less compact than that of black skin [53]. In white skin, the papillary and reticular layers of the dermis are more distinct, contain larger collagen fiber bundles, and the fiber fragments are sparse. The dermis of black skin contains closely stacked, smaller collagen fiber bundles with a surrounding ground substance. The fiber fragments are more prominent in black skin than in white skin. One study showed on histological examinations that African skin type had greater convoluted appearance of the dermal-epidermal junction (DEJ) than the Caucasian skin type. This same study also revealed on immunostaining that laminin 332, type IV and VII collagens, and nidogen proteins at the DEJ were lower in African skin compared with Caucasian skin [54]. While the quantity is similar in both black and white skin, the size of melanophages is larger in black skin. Also, the number of fibroblasts and lymphatic vessels is greater in black skin. The fibroblasts are larger, have more biosynthetic organelles, and are more multinucleated in black skin [7]. The lymphatic vessels are dilated and empty with surrounding elastic fibers [53]. No racial differences in the epidermal nerve fiber network have been observed using laser-scanning confocal microscopy, suggesting that there is no difference in sensory perception between races, as suggested by capsaicin response to C-fiber activation [55].

Skin extensibility is how stretchable the skin is. Elastic recovery is the time required for the skin to return to its original state after releasing the stretched skin. Skin elasticity is elastic recovery divided by extensibility. Studies that investigated skin extensibility, elastic recovery, and skin elasticity between races yield conflicting results [34, 56]. It is likely that elastic recovery and extensibility vary by anatomic site, race, and age.

Intrinsic skin aging in ethnic skin

The majority of literature regarding facial aging features Caucasian patients. Facial aging is the result of the combination of photodamage, fat atrophy, gravitational soft tissue redistribution, and bone remodeling. Figure 3.1 demonstrates the morphologic changes of the face caused by aging. The onset of morphologic aging appears in the upper face during the thirties and gradually progresses to the lower face and neck over the next several decades [57].

Early signs of facial aging occur in the periorbital region. In the late thirties, brow ptosis, upper eyelid skin laxity, and descent of the lateral portion of the eyebrow ("hooding") lead to excess skin of the upper eyelids. During the mid-forties, "bags" under the eyes result from weakening of the inferior orbital septum and prolapse of the underlying intraorbital fat. Lower eyelid fat prolapse may occur as early as the second decade in those with a familial predisposition. Photodamage produces periocular and brow rhytides [57]. The periorbital and midface regions in skin of color tend to have more pronounced signs of facial aging as compared with the upper third of the face. There is also a decreased tendency toward perioral rhytides and radial lip lines in skin of color [58].

Brow ptosis in African-Americans appears to occur to a lesser degree and in the forties opposed to the thirties compared to that in whites [59]. Prolapse of the lacrimal gland may masquerade as lateral upper eyelid fullness in African-Americans [60]. For Hispanics, the brow facial soft tissues sag at an earlier age [61]. In Asians, the descent of thick juxtabrow tissues in the lateral orbit coupled with the absences of a supratarsal fold may create a prematurely tired eye [57].

The midface showed signs of aging during the forties. The malar soft tissue adjacent to the inferior orbital rim descends,

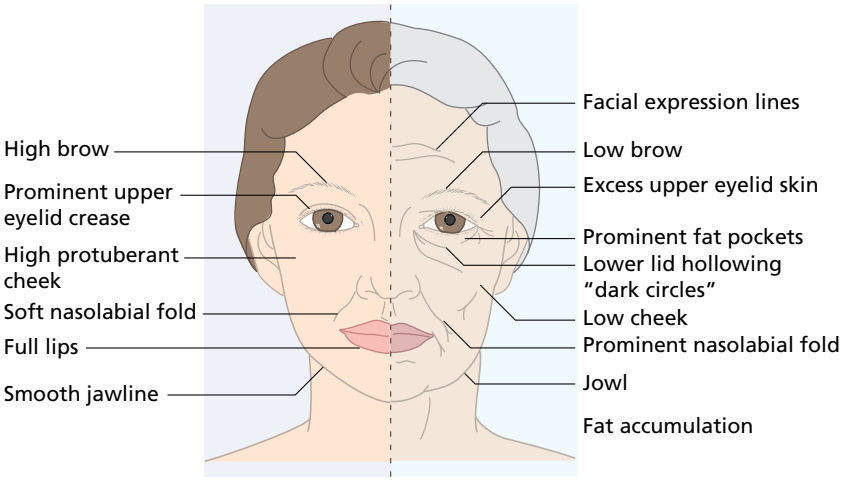

Figure 3.1 Morphologic signs of aging. (Source: Halder, 2006 [57]. Reproduced with permission of Taylor & Francis.)

accumulating as fullness along the nasolabial fold. The malar soft tissue atrophy and ptosis result in periorbital hollowing and tear through deformity. Early aging is evident in individuals of African, Asian, and Hispanic origin in the midface region more so than in the upper or lower regions. Signs include tear trough deformity, infraorbital hollowing, malar fat ptosis, nasojugal groove prominence, and deepening of the nasolabial fold. This predisposition to midface aging is likely the result of the relationship of the eyes to the infraorbital rim, basic midface skeletal morphology, and skin thickness [57].

The soft tissue of the lower face is supported in a youthful anatomic position by a series of retaining ligaments within the superficial musculoaponeurotic system (SMAS) [62]. The SMAS is a discrete fascial layer that envelops the face and forms the basis for resuspending sagging facial tissues [17]. The SMAS fascia envelope maintains tension on facial muscles and offsets soft tissue sagging. In the late thirties, gradual ptosis of the SMAS and skin elastosis sets the stage for jowl formation. Accumulation of submandibular fat and a sagging submandibular gland may have a role in interrupting the smooth contour of a youthful jawline. Changes in the lower face lead to changes in the neck because the SMAS is anatomically continuous with the platysma muscle. Sagging of the SMAS–platysma unit and submandibular fat redistribution gradually blunts the junction between the jaw and neck. A "double chin" appears at any age as a result of cervicomental laxity with excess submental fat deposits. During the fifties, diastasis and hypertrophy of the anterior edge of the platysma muscle may produce vertical banding in the cervicomental area. During the sixth, seventh, and eighth decades, progressive soft tissue atrophy and bony remodeling of the maxilla and mandible create a relative excess of sagging skin, further exaggerating facial aging. Jowling is a sign of lower facial aging in black persons [57]. In some cases, a bony chin underprojection make create excess localized submental fatty deposits despite a smoothly contoured jawline. However, in Asians, jowl formation may result from fat accumulation in the buccal space [57]. The "double chin" is more common in Caucasians under 40 years of age than Asians of the same age group, but more common in Asians over 40 years of age because of redundant cervical skin [63].

Extrinsic aging (photoaging) of ethnic skin

Sunlight is a major factor for the appearance of premature aging, independent of facial wrinkling, skin color, and skin elasticity. By the late forties, individuals with greater sun exposure appear older than those with less sun exposure. However, the perceived age of individuals in their late twenties is unaffected by sun exposure. Solar exposure greatly increases the total wrinkle length by the late forties. The extent of dermal degenerative change seen by the late forties correlates with premature aging. There is a high correlation between perceived age and facial wrinkles; perceived age and elastosis; and perceived age and the quantity of collagen. The grenz zone is a subepidermal band of normal dermis consisting of normal collagen fibers and thought to be a site of continual dermal repair. The grenz zone becomes visually apparent only after there is sufficient elastotic damage. With progressive elastosis, the grenz zone becomes thinner [64].

Histopathology

Epidermis

The absolute number of Langerhans cells varies from person to person but chronic sun exposure decreases their number or depletes them [65]. The severely sun-damaged skin has many vacuolated cells in the spinous layer, excessively vacuolated basal keratinocytes and melanocytes, cellular atypia, and loss of cellular polarity. Apoptosis in the basal layer is increased. A faulty stratum lucidum and horny layer result from intracellular vesicles in the cells of the basal and spinous layers (sunburn cells), apoptosis, and dyskeratosis. There is focal necrobiosis in the epidermis and dermis in sun-exposed skin. While histologic findings of photoaging in white sun-exposed skin include a distorted, swollen, and distinctly cellular stratum lucidum, the stratum lucidum of African-American sun-exposed skin remains compact and unaltered [7]. The stratum lucidum in black skin is not altered by sunlight exposure [7].

With age, the dermoepidermal junction becomes flattened with multiple zones of basal lamina and anchoring fibril reduplication. Microfibrils in the papillary dermis become more irregularly oriented. Compact elastic fibers show cystic changes and separation of skeleton fibers with age. The area occupied by the superficial vascular plexus in specimens of equal epidermal surface length decreases from the infant to young adult (21–29 years) to adult (39–52 years) age groups, then increased in the elderly adult (73–75 years) age group [66]. With the exception of the vascularity in the elderly adult group, the above features are similar to those seen in aging white skin and suggest that chronological aging in white and black skin is similar. Oxytalan fibers are found in the papillary dermis of sun-exposed skin of white individuals in their twenties and early thirties but disappear in the forties. In black skin, the oxytalan fibers are still found in the dermis of individuals in their fifties. No solar elastosis is seen in specimens of black sun-exposed skin. Older black subjects have an increased number and thickness of elastic fibers that separate the collagenous fiber layer in the reticular dermis. The sun-exposed skin of a 45-year-old light-complexioned black female shared the same amount and distribution of elastic fibers as those in white sun-exposed skin [7].

The grenz zone consists of small fibers oriented horizontally and replaces the papillary dermis. When elastotic material accumulates in the dermis, it crowds out all the collagenous fibers, which are resorbed. As the elastic material is resorbed, wisps of collagenous fibers form in its place. Widely spaced, larger collagenous fiber bundles lie between the waning elastotic masses. The total volume of the dermis gradually diminishes as the spaces between the remaining collagenous and elastic fibers are reduced. When the epidermis rests directly on top of the horizontally oriented, medium-sized collagenous fiber bundles of the intermediate dermis, the dermis lacks a papillary and grenz zone and the dermis cannot sufficiently support the epidermis. As a result, the shrinking dermis crinkles and small wrinkles form. This may be the reason for the absence of a structural basis in secondary wrinkles and may explain why wrinkles flatten out when fluids are injected into the skin or when edema occurs [65].

Photoaging in skin of color has variable presentations. Wrinkling is not as common a manifestation of photoaging in black persons, South Asians, or darker complexioned Hispanics as in white persons because of the photoprotective effects of melanin. All racial groups are eventually subjected to photoaging. Within most racial groups, the lighter complexioned individuals show evidence of photodamaged skin. Caucasian skin has an earlier onset and greater skin wrinkling and sagging signs than darker skin types. Visual photoaging assessments reveal that white skin has more severe fine lines, rhytides, laxity, and overall photodamage than African-American skin [47].

Photoaging is uncommon in black persons but is more often seen in African-Americans than in Africans or Afro-Caribbeans. The reason may be the heterogeneous mixture of African, Caucasian, and Native American ancestry often seen in African-Americans. In African-Americans, photoaging appears primarily in lighter complexioned individuals and may not be apparent until the late fifth or sixth decades of life [67]. Photoaging in this group appears as fine wrinkling and mottled pigmentation. In spite of the photoprotective effects of melanin, persons of skin of color are still prone to photoaging, but the reason is not completely known. Infrared radiation may also contribute to photodamage. There is evidence that chronic exposure to natural or artificial heat sources can lead to histologic changes resembling that of UV-induced changes, such as elastosis and carcinoma [68]. The pigmentary manifestations of photoaging common in skin of color include seborrheic keratoses, actinic lentigines, mottled hyperpigmentation, and solar-induced facial melasma [69]. However, African-American skin has greater dyspigmentation, with increased hyperpigmentation and unevenness of skin tone [46].

Hair

There are two types of hair fibers: terminal and vellus. Terminal hair is found on the scalp and trunk. Vellus hair is fine and shorter and softer than terminal hair. The hair fiber grows from the epithelial follicle, which is an invagination of the epidermis from which the hair shaft develops via mitotic activity and into which sebaceous glands open. The hair follicle is one of the most proliferative cell types in the body and undergoes growth cycles. The cycles include anagen (active growth), catagen (regression), and telogen (rest). Each follicle follows a growth pattern independent of the rest. The hair follicle is lined by a cellular inner and outer root sheath of epidermal origin and is invested with a fibrous sheath derived from the dermis. Each hair fiber is made up of an outer cortex and a central medulla. Enclosing the hair shaft is a layer of overlapping keratinized scales, the hair cuticle that serves as protective layers.

Racial differences in hair include the hair type, shape, and bulb. There are four types of hair: helical, spiral, straight, and wavy. The spectrum of curliness is displayed in Figure 3.2. The

Figure 3.2 The spectrum of curliness in human hair. (Source: Loussouarn *et al.*, 2007 [*Int J Dermatol* **46** (Suppl 1), 2–6]. Reproduced with permission of John Wiley & Sons.)

vast majority of black persons have spiral hair [70]. The hair of black persons is naturally more brittle and more susceptible to breakage and spontaneous knotting than that of white persons. The kinky form of black hair, the weak intercellular cohesion between cortical cells, and the specific hair grooming practices among black persons account for the accentuation of these findings [70]. The shape of the hair is different between races: black hair has an elliptical shape, Asian hair is round-shaped straight hair, and Caucasian hair is intermediate [71, 72]. The bulb determines the shape of the hair shaft, indicating a genetic difference in hair follicle structure [33]. The cross-section of black hair has a longer major axis, a flattened elliptical shape, and curved follicles. Asian hair has the largest cross-sectional area and Western European hair has the smallest [72, 73]. Black persons have fewer elastic fibers anchoring the hair follicles to the dermis than white subjects. Melanosomes were in the outer root sheath and in the bulb of vellus hairs in black, but not in white persons. Black hair also has more pigment and on microscopy has larger melanin granules than hair from light-skinned and Asian individuals. Similarities between white and black hair include cuticle thickness, scale size and shape, and cortical cells [73].

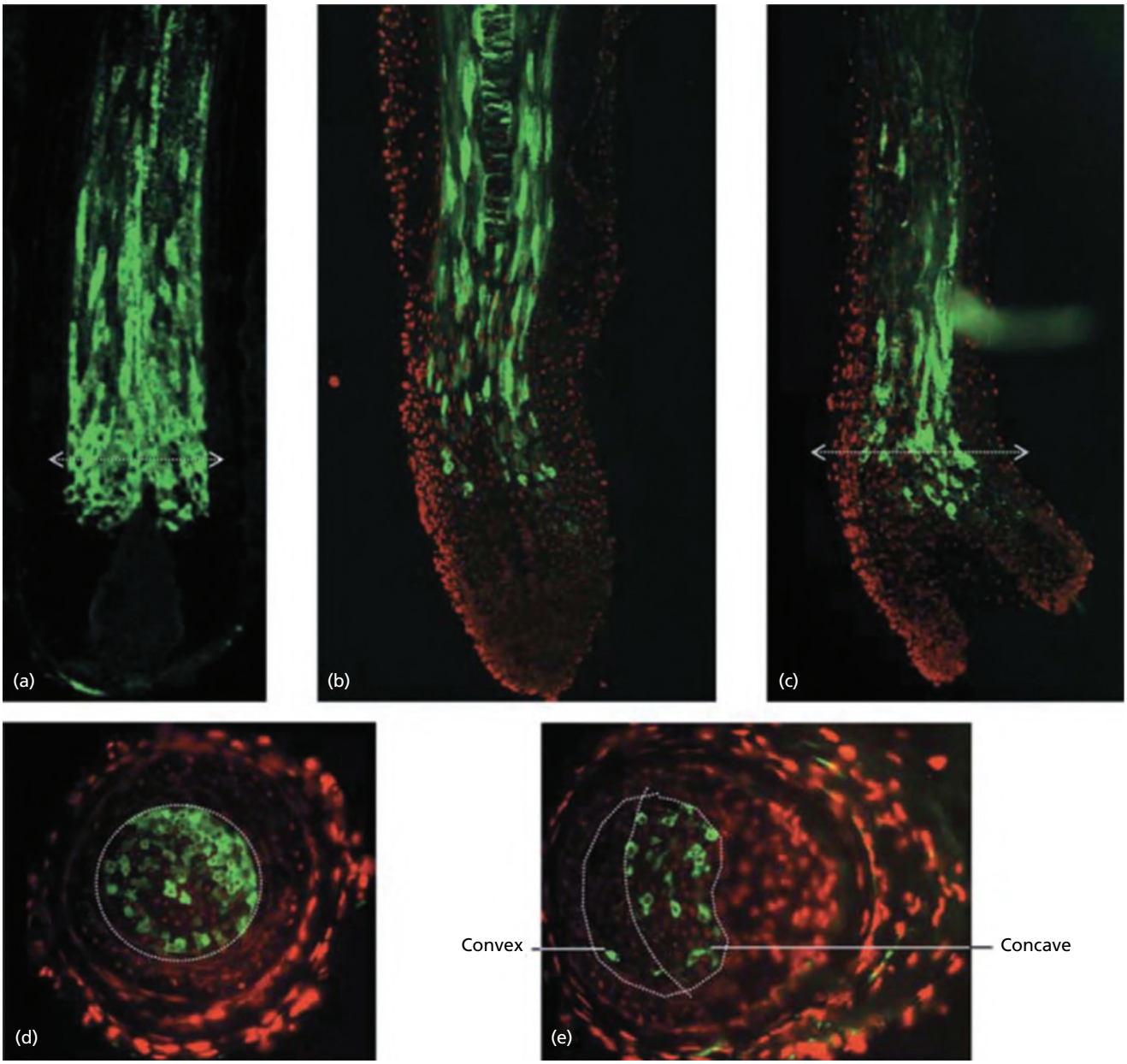

Figure 3.3 K38 hair keratin distribution in hair follicles. K38 pattern in (a) straight, (b) wavy, and (c) curly hair longitudinal sections. K38 pattern in (d) straight and (e) curly hair cross-sections. (Source: Thibaut *et al.*, 2007 [74]. Reproduced with permission of John Wiley & Sons.)

While the curly nature of black hair is believed to result from the shape of the hair follicle [73], research has shown that the curliness of hair correlates with the distribution of cortical cells independent of ethnoracial origin [74]. Black hair follicles have a helical form, whereas the Asian follicle is completely straight and the Caucasian hair form is intermediate [73]. Mesocortical, orthocortical, and paracortical cells are the three cell types in the hair cortex. In straight hair, mesocortical cells predominate [74]. In wavy hair, the orthocortical and mesocortical cells are interlaced around paracortical cells. In tightly curled hair, the mesocortex disappears, making orthocortical cells the majority. Distinct cortical cells express the acidic hair keratin K38. Figure 3.3 displays the distribution of K38 cells in straight, wavy, and tightly curled hair. Straight hair has a patchy but homogenous pattern of positively charged K38cells surrounding a core of negatively charged cells. As the degree of curl decreases, the K38pattern becomes asymmetric, independent of ethnic origin. In tightly curled hair, K38 accumulates on the concave side of the hair fiber and the medulla compartment disappears.

There are no differences in keratin types between hair from different races and no differences in amino acid composition of hair from different races [75]. Among Caucasian, Asian, and Africans, there are no differences in the intimate structures of fibers, whereas geometry, mechanical properties, and water swelling differed according to ethnic origin [76]. One study [77] in 1941 did find variation in the levels of some amino acids between black and white hair. Black subjects had significantly greater levels of tyrosine, phenylalanine, and ammonia in the hair but were deficient in serine and threonine.

The morphologic features of African hair were examined using the transmission and scanning electron microscopic (SEM) techniques in an unpublished study. The cuticle cells of African hair were compared with those of Caucasian hair. Two different electronic density layers were shown. The denser exocuticle is derived from the aggregation of protein granules that first appear when the scale cells leave the bulb region. The endocuticle is derived from the zone that contains the nucleus and cellular organites. The cuticle of Caucasian hair is usually 6–8 layers thick and constant in the hair perimeter, covering the entire length of each fiber. However, black hair has variable thickness; the ends of the minor axis of fibers are 6–8 layers thick, and the thickness diminishes to 1–2 layers at the ends of the major axis. The weakened endocuticle is subject to numerous fractures (Handjur C, Fiat, Huart M, Tang D, Leory F, unpublished data).

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CHAPTER 4

The Somatosensory System and Sensitive Skin

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BASIC CONCEPTS

- The primary sensory modality subserving the body senses is collectively described as the somatosensory system and comprises all those peripheral afferent nerve fibers, and specialized receptors, subserving cutaneous, and proprioceptive sensitivity.
- Individuals with sensitive skin demonstrate heightened reactivity of the cutaneous somatosensory system.
- A separate set of neurons mediates itch and pain. The afferent neurons responsible for histamine-induced itch in humans are unmyelinated C-fibers.
- Low threshold mechanoreceptors are responsible for the sensation of touch, a wide range of receptor systems code for temperature, and as the skin's integrity is critical for survival, there are an even larger number of sensory receptors and nerves that warn us of damage to the skin.
- With the recent discovery of a class of neurons that respond optimally to gentle stroking touch (sharing commonality with the itch and pain nerves), our understanding of the skin's sensitivity is entering a new chapter.

Introduction

The primary sensory modality subserving the body senses is collectively described as the somatosensory system and comprises all those peripheral afferent nerve fibers, and specialized receptors, subserving cutaneous, and proprioceptive sensitivity. The latter processes information about limb position and muscle forces which the central nervous system uses to monitor and control limb movements and, via elegant feedback and feedforward mechanisms, ensure that a planned action or movement is executed fluently. This chapter focuses on sensory inputs arising from the skin surface – cutaneous sensibility – and describes the neurobiological processes that enable the skin to "sense." Skin sensations are multimodal and are classically described as sensing the four submodalities of touch, temperature, itch, and pain. We also consider the growing evidence for a fifth submodality, present only in hairy skin, which is preferentially activated by slowly moving, low force, mechanical stimuli.

This brief introduction to somatosensation starts with the discriminative touch system. Sensation enters the peripheral nervous system via sensory axons that have their cell bodies sitting just outside the spinal cord in the dorsal root ganglia, with one ganglion for each spinal nerve root. Neurons are the building blocks of the nervous system and somatosensory neurons are unique in that, unlike most neurons, the electrical signal does not pass through the cell body but the cell body sits off to one side, without dendrites. The signal passes directly from the distal axon process to the proximal process which enters the dorsal half of the spinal cord, and immediately turns up the spinal cord forming a white matter column, the dorsal columns, which relay information to the first brain relay nucleus in the medulla. These axons are called the primary afferents, because they are the same axons that carry the signal into the spinal cord. Sensory input from the face does not enter the spinal cord but instead enters the brainstem via the trigeminal nerve (one of the cranial nerves). Just as with inputs from the body, there are four modalities of touch, temperature, itch, and pain, with each modality having different receptors traveling along different tracts projecting to different targets in the brainstem. Once the pathways synapse in the brainstem, they join those from the body on their way up to a relay in the thalamus and then on to higher cortical structures. Sensory information arising from the skin is represented in the brain in the primary and secondary somatosensory cortex, where the contralateral body surfaces are mapped in each hemisphere.

Cosmetic Dermatology: Products and Procedures, Third Edition. Edited by Zoe Diana Draelos.

Peripheral nervous system

The skin is the most extensive and versatile organ of the body and in a fully grown adult covers a surface area approaching 2 m^2. This surface is far more than just a passive barrier. It contains in excess of two million sweat glands and five million hairs covering all surfaces, apart from the soles of the feet and the palms of the hands (glabrous skin). Evidence is also emerging that nonglabrous skin contains a system of nerves that code specifically for the pleasant properties of touch. Skin consists of an outer, waterproof, stratified squamous epithelium of ectodermal origin – the epidermis – plus an inner, thicker, supporting layer of connective tissue of mesodermal origin – the dermis. The thickness of this layer varies from 0.5 mm over the eyelid to >5.0 mm over the palm and sole of the foot.

Touch

Of the four "classic" submodalities of the somatosensory system, discriminative touch subserves the perception of pressure, vibration, and texture and relies upon four different receptors in the digit skin:

1. Meissner corpuscles;
2. Pacinian corpuscles;
3. Merkel disks; and
4. Ruffini endings.

These are collectively known as low threshold mechanoreceptors (LTMs), a class of cutaneous receptors that are specialized to transduce mechanical forces impinging the skin into nerve impulses. The first two are classified as fast adapting (FA) as they only respond to the initial and final contact of a mechanical stimulus on the skin, and the second two are classified as slowly adapting (SA) as they continue firing during a constant mechanical stimulus. A further classification relates to the LTM's receptive field (RF; i.e. the surface area of skin to which they are sensitive). The RF is determined by the LTM's anatomic location within the skin, with those near the surface at the dermal–epidermal boundary, Meissner corpuscles, and Merkel disks, having small RFs, and those lying deeper within the dermis, Pacinian corpuscles (PC), and Ruffini endings, having large RFs (Figure 4.1).

Psychophysical procedures have been traditionally employed to study the sense of touch where differing frequencies of vibrotactile stimulation are used to quantify the response properties of this sensory system. Von Bekesy [1] was the first to use vibratory stimuli as an extension of his research interests in audition. In a typical experiment, participants were asked to respond with a simple button-press when they could just detect the presence of a vibration presented to a digit, within one of two time periods. This two-alternative force choice (2-AFC) paradigm provides a threshold-tuning curve, the slopes of which provide information about a particular class of LTM's response properties.

Bolanowski et al. [2] proposed that there are four distinct psychophysical channels mediating tactile perception in the glabrous skin of the hand. Each psychophysically determined channel is represented by one of the four anatomic end organs and nerve fiber subtypes, with frequencies in the 40–500 Hz range providing a sense of "vibration," transmitted by PC (PC channel or FAI); Meissner corpuscles being responsible for the sense of "flutter" in the 2–40 Hz range (NPI channel or FAII); the sense of "pressure" being mediated by Merkel disks in the 0.4–2.0 Hz range (NPIII or SAI); and Ruffini end organs producing a "buzzing" sensation in the 100–500 Hz range (NPII or SAII). Neurophysiologic studies support this model, but there is still some way to go to link the anatomy with perception (Table 4.1).

There have been relatively few studies of tactile sensitivity on hairy skin, the cat being the animal of choice for most of these studies. Mechanoreceptive afferents (Aβ fibers) have been described that are analogous to those found in human glabrous skin (FAI, FAII, SAI, SAII), and Essick and Edin [3] have described sensory fibers with these properties in human facial skin. The relationship between these sensory fibers and tactile perception is still uncertain.

Sensory axons are classified according to their degree of myelination, the fatty sheath that surrounds the nerve fiber. The degree of myelination determines the speed with which the axon can conduct nerve impulses and hence the nerves conduction velocity. The largest and fastest axons are called Aα and include some of the proprioceptive neurons, such as the muscle stretch receptors. The second largest group, called Aβ, includes all of the discriminative touch receptors being described here. Pain, itch, and temperature include the third fourth and fifth groups, Aδ and C-fibers.

Electrophysiological studies on single peripheral nerve fibers innervating the human hand have provided a generally accepted model of touch that relates the four anatomically defined types of cutaneous or subcutaneous sense organs to their neural response patterns [4]. The technique used in these studies is called microneurography and involves inserting a fine tungsten microelectrode, tip diameter <5 μm, through the skin and into the underlying median nerve which innervates the thumb and first two digits (Figure 4.2).

Temperature

The cutaneous somatosensory system detects changes in ambient temperature over an impressive range, initiated when thermal stimuli that differ from a homeostatic set-point excite temperature-specific sensory nerves in the skin and relay this information to the spinal cord and brain. It is important to recognize that these nerves code for temperature change, not absolute temperature, as a thermometer does. The system does not have specialized receptor end organs such as those found with LTMs but uses free nerve endings throughout skin to sense changes in temperature. Within the innocuous thermal sensing range, there are two populations of thermosensory fibers, one that responds to warmth (warm receptors) and one that responds to cold (cold receptors), and include fibers from the Aδ and C range. Specific cutaneous cold and warm receptors have been

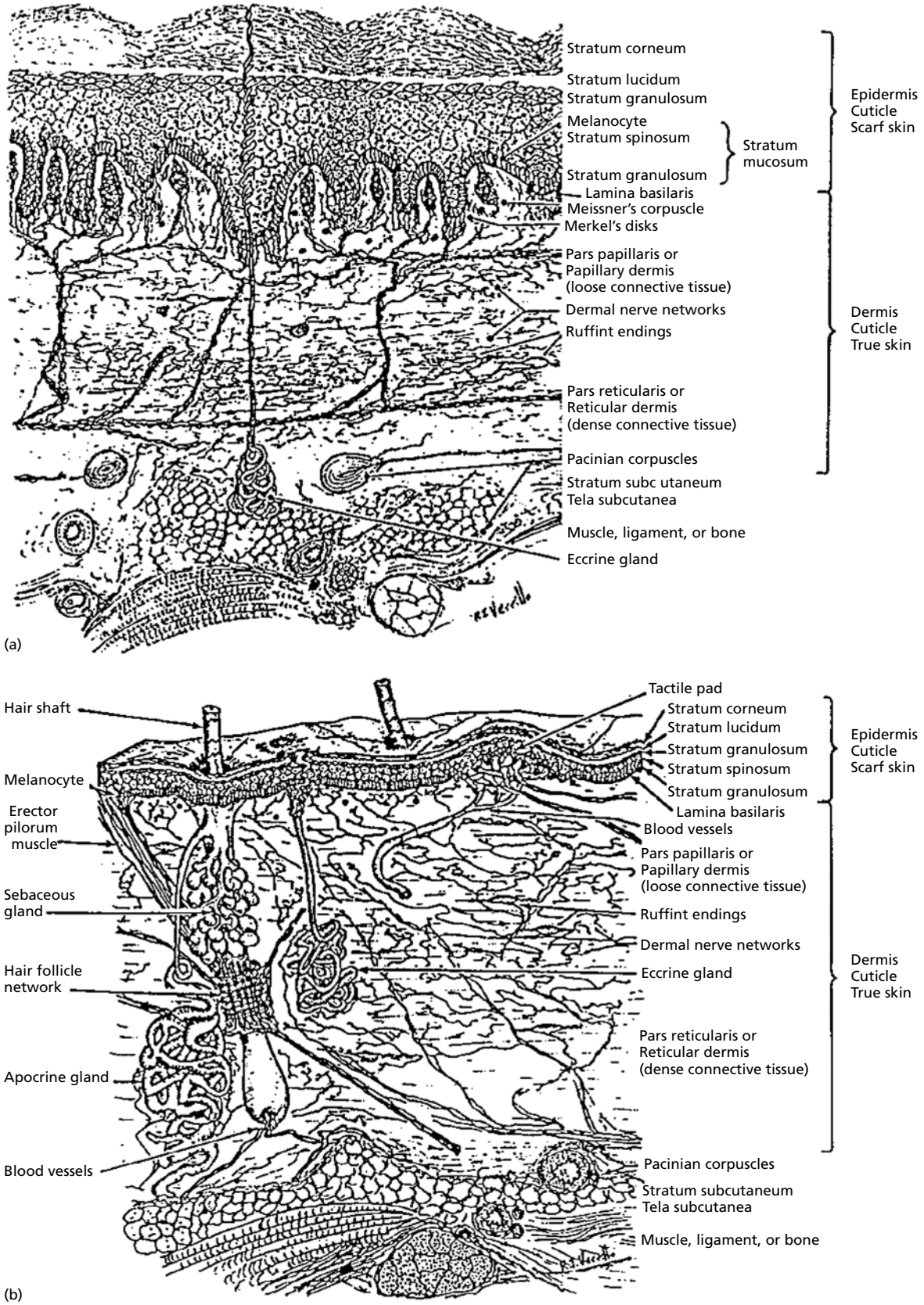

Figure 4.1 A cross-sectional perspective of (a) glabrous and (b) hairy skin. (Source: R.T. Verrillo, artist. Reproduced with permission.)

defined as slowly conducting units that exhibit a steady-state discharge at constant skin temperature and a dynamic response to temperature changes [6, 7]. Cold-specific and warm-specific receptors can be distinguished from nociceptors that respond to noxious low and high temperatures <20 °C and >45 °C) [8, 9], and also from thermosensitive mechanoreceptors [6, 10]. Standard medical textbooks describe the cutaneous cold sense in humans as being mediated by myelinated A-fibers with CVs in the range 12–30/ms [11], but recent work concludes that either human cold-specific afferent fibers are incompletely myelinated "BC" fibers, or else there are C as well as A cold fibers, with the C-fiber group contributing little to sensation (Figure 4.3) [12].

Table 4.1 Main characteristics of primary sensory afferents innervating human skin.

Class	Modality	Axonal diameter (μm)	Conduction velocity (m/s)
Myelinated			
Aα	Proprioceptors from muscles and tendons	20	120
Aβ	Low threshold mechanoreceptors	10	80
Aδ	Cold, noxious, thermal	2.5	12
Unmyelinated			
C-pain	Noxious, heat, thermal	1	<1
C-tactile	Light stroking, gentle touch	1	<1
C-tutonomic	Autonomic, sweat glands, vasculature	1	<1

The free nerve endings for cold-sensitive or warm-sensitive nerve fibers are located just beneath the skin surface. The terminals of an individual temperature-sensitive fiber do not branch profusely or widely. Rather, the endings of each fiber form a small, discretely sensitive point, which is separate from the sensitive points of neighboring fibers. The total area of skin occupied by the receptor endings of a single temperature-sensitive nerve fiber is relatively small (approximately 1 mm in diameter), with the density of these thermosensitive points varying in different body regions. In most areas of the body, there are 3–10 times as many cold-sensitive points as warm-sensitive points. It is well established from physiologic and psychologic testing that warm-sensitive and cold-sensitive fibers are distinctively different from one another in both structure and function.

Pain

Here, we consider a system of peripheral sensory nerves that innervate all cutaneous structures and whose sole purpose is to protect the skin against potential or actual damage. These primary afferents include Aδ and C-fibers which respond selectively and linearly to levels of thermal, mechanical, and chemical stimuli that are tissue-threatening. This encoding mechanism is termed nociception and describes the sensory process detecting any overt, or impending, tissue damage. The term pain describes the perception of irritation, stinging, burning, soreness, or

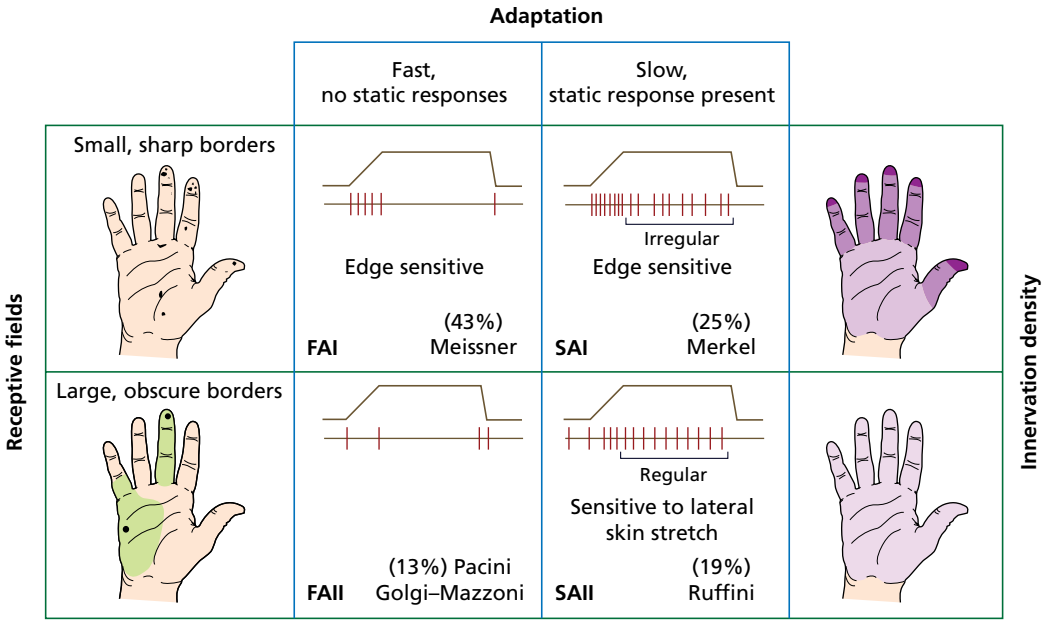

Figure 4.2 The four types of low threshold mechanoreceptors in human glabrous skin are depicted. The four panels in the center show the nerve firing responses to a ramp and hold indentation and the frequency of occurrence (%) and putative morphologic correlate. The black dots in the left panel show the receptive fields of type I (top) and type II (bottom) afferents. The right panel shows the average density of type I (top) and type II (bottom) afferents with darker area depicting higher densities. (Source: Westling, 1986 [5]. Reproduced with permission.)